National Cancer Institute

Center for Cancer Research

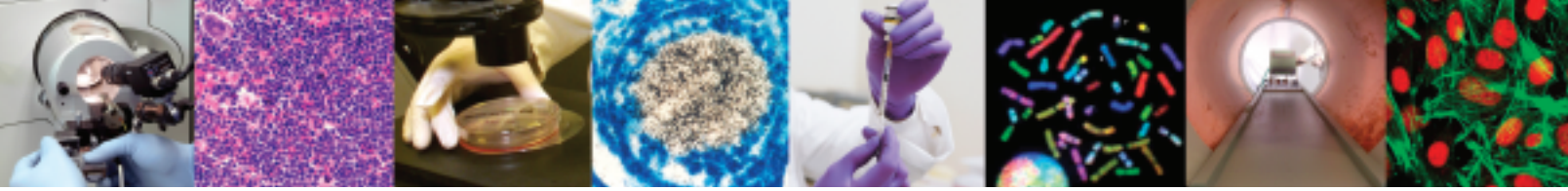
explore
discover
translate

Volume 2

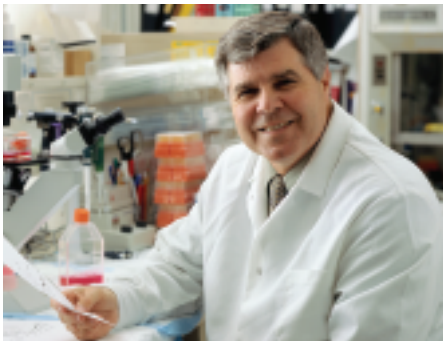
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

"If you look at discovery, most things—in one way or another—have come out of, or were somehow touched by, the intramural program."

John E. Niederhuber, M.D.
Director, National Cancer Institute



From the CCR Director



The National Cancer Institute's Center for Cancer Research (CCR) is a comprehensive translational research program focused on moving discoveries between the laboratory and the clinic to benefit both cancer and AIDS patients. Our sustained commitment to basic research and to innovative technology development has accelerated our progress in finding new approaches to cancer prevention, detection, diagnosis, and treatment. The agile infrastructure that exists in CCR fosters this progress by supporting both investigator-initiated research and programmatic efforts that harness the expertise of our highly acclaimed researchers through the formation of multidisciplinary translational research teams. Collaborations come easily within this dynamic environment, enabling seamless transitions from exploration, to discovery, to translation.

The CCR provides sustained support for outstanding, rigorously reviewed, investigator-initiated research programs. This research is spearheaded by the scientist and addresses some of the most perplexing questions in scientific research today. Our researchers apply their expertise, insights, and research passion to solving these complex questions and translating them into interventions for cancer and AIDS. The characteristic ability of our investigators to navigate and tame the uncharted regions of exploration and discovery is exemplified by the recent election of Dr. Carl Wu to the National Academy of Sciences. Dr. Wu joins seven other distinguished CCR scientists who have been honored by the Academy for making major contributions to biomedical research. These individuals have provided fundamental insights and principles that serve as intellectual landmarks and are critical for guiding subsequent research.

CCR's distinctive ability to integrate multiple scientific disciplines and approaches in support of scientific discovery is another invaluable characteristic of our research program. Our Centers of Excellence, Faculties, Working Groups, and Programs successfully cut across organizational boundaries to foster collaborative research. The newly formed Center of Excellence in Chromosome Biology (CECB) is one example of such an effort. The interactive nature of the CECB is already accelerating advances in the critical area of modern molecular biology and chromosome dynamics as it relates to cancer research. The Redox Biology Faculty is an excellent example of team science catalyzing cross-cutting collaboration among biochemists, chemists, clinical oncologists, epidemiologists, and others interested in the molecular mechanisms of redox stress and its effect on cancer's progression.

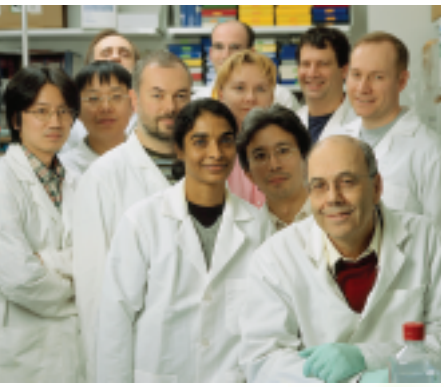
Major areas of focus within the CCR include molecular oncology and molecular targets, cancer biology and etiology, HIV/AIDS, immunology, genetics and genomics, and imaging and biomarkers. Transcending the borders of these focus areas, CCR's programmatic initiatives capture strengths within these theme areas and combine them to generate new ideas, collaborations, and outcomes. In the months ahead, specific emphasis will placed on the translational inflammation and cancer initiative, a cutting-edge angiogenesis research program, a joint program in early therapeutics development, increased activity in cancer stem cell research, and an integrated imaging program that will extend from molecular- and nano-scale approaches to noninvasive imaging techniques to benefit patients.

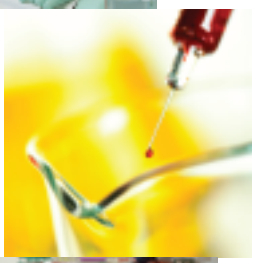
Taking time to acknowledge and reflect on the many advances that have already been made within the CCR is critical as these achievements serve as the foundation for continued scientific excellence. The highlights featured on the following pages demonstrate how CCR's sustained commitment to exploration and discovery lead to new approaches and interventions to improve the lives of cancer and HIV/AIDS patients.

Robert H. Wiltrout, PhD.
Director, Center for Cancer Research
National Cancer Institute
National Institutes of Health

Introduction

The CCR promotes a collaborative research environment, which is integral to accelerating scientific progress.





HISTORY

The National Cancer Institute (NCI) was the first Institute created at the National Institutes of Health (NIH) in 1937. Its intramural research team was assembled in 1939 through a merger of the Office of Cancer Investigations at Harvard University and a Washington, DC-based pharmacology division of the NIH. Both labs relocated to Bethesda. In 1948, the NCI was organized into three units: cancer control, intramural research, and extramural research. Soon after the National Cancer Act was signed into law in 1971, empowering NCI leadership to direct the National Cancer Program, the intramural program expanded under the Division of Cancer Treatment. Then, during a major reorganization of NCI in 1996, two new intramural divisions arose: Clinical Science and Basic Science. In 2001, these two Divisions merged into today's Center for Cancer Research, where basic and clinical science are seamlessly integrated with a mission to reduce the burden of cancer through exploration, discovery, and translation.

VISION

At CCR, we envision providing all cancer patients better options for cancer prevention, detection, diagnosis, and treatment. We focus on basic, translational, and clinical research with potential for yielding new scientific knowledge seminal discoveries that will benefit cancer patients. We translate novel therapies, approaches, and technologies into effective care for the patients in our clinical trials. We deliver our discoveries as meaningful advances that improve public health. We strive to see that all who could possibly benefit from participation in our early-phase clinical trials are able to do so. As advances are made in our studies, we communicate them quickly and encourage broad incorporation across the oncology community to ensure better care for all patients. These efforts, and the dedication of purpose that drives our vision, will continue to be hallmarks of our work.

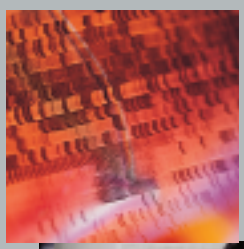
VALUES

A commitment to scientific excellence and integrity serves as CCR's foundation. This sense of obligation is held individually and reflected collectively as we strive to fulfill our purpose in addressing emerging needs within cancer research in this country. We are committed to making meaningful progress solely for the greater public good—improving compassionate and effective care for all cancer patients.

CULTURE

The CCR promotes a collaborative research environment, which is integral to accelerating scientific progress. Our focus areas give us the flexibility to reassess and respond rapidly to emerging scientific needs and opportunities, leveraging strengths of experts from diverse fields. This approach enables us to complement and interface with the activities of the extramural cancer research community. We are well poised to tackle complex scientific questions related to cancer and generate answers that will ultimately benefit patients and the public.

Doing Science at the CCR



A Lifelong Dedication to Patients

THE SURGEON AS MENTOR

Mentorship is a central feature of Dr. Rosenberg's medical practice. For more than 20 years, he has run the National Cancer Institute's Fellowship Program in Surgical Oncology, training more than four dozen of today's Chiefs of Surgical Oncology nationwide. He shares his surgical skills and his passion to develop effective treatments for patients with cancer.

Dr. Steven A. Rosenberg has spent his 34-year career at NCI intent on rallying the immune system to rise up and fight back against invading cancer. His undaunted pursuit has helped launch the field of cancer immunotherapy.

"The body recognizes a cancer as foreign, but not foreign enough to reject it," explains Dr. Rosenberg. "The goal of immunotherapy is to see if we can enhance the body's defenses to fight the invading cancer." He became committed to this notion as a surgical resident at Brigham Hospital in Boston, when he removed a gall bladder from a patient who, 12 years earlier, had been sent home with an untreatable, aggressive stomach cancer. That patient's own body had cured his cancer. "Something began to burn in me, something that has never gone away," said Dr. Rosenberg.

"From the time I stopped wanting to be a cowboy, I wanted to be a doctor and do research. I wanted to find things that no one else knew. I always had this desire—no, an obsession—with doing something that would alleviate suffering."

Steven A. Rosenberg, M.D., Ph.D.
Chief of CCR's Surgery Branch

That internal fire has carried him through scores of attempts to replicate what he saw in that patient almost 40 years ago. There were many setbacks along the way. But these efforts—including his work in gene therapy and interleukin-2 (IL-2) development—have all informed his current, most promising approach, called adoptive cell transfer. His clinical trials of the technique have provided "far and away the most convincing evidence that the immune system can successfully fight cancer," he says.

In 1985, Dr. Rosenberg was the first to demonstrate that IL-2 could stimulate regression of metastatic tumors. IL-2 is a protein produced by the body that boosts the immune system and stimulates the growth of several immune cells, including T lymphocytes. The Food and Drug Administration approved IL-2 as a treatment for patients with metastatic renal cell cancer in 1992 and as a treatment for melanoma in 1998. Today, it is part of standard therapy for certain patients with these cancers.

In 1989, Dr. Rosenberg helped usher in the era of gene therapy as the leader of the team that gave genetically engineered

Dr. Rosenberg's impact has been substantial. He has authored eight books and over 900 scientific articles covering various aspects of cancer research. Dr. Rosenberg was the most cited clinician in the world in the field of oncology for the 17 years between 1981 to 1998 (ISI, 1999). *Photo credit: Rhoda Baer*

"CCR represents a marriage between basic science and clinical care that exists nowhere else in the world, Dr. Rosenberg says. "We are able to perform very sophisticated lab manipulations and bring them to patients a few dozen yards down the hall. Our mandate is to make progress and bring cutting-edge science to help patients with desperate illnesses."

lymphocytes—containing a retroviral vector carrying a bacterial marker gene—to cancer patients receiving cell transfer therapy. This was the first time a foreign gene was inserted into humans and led a year later to trials conducted with Drs. French Anderson and Michael Blaese, who gave a 4-year-old girl with ADA-deficient severe combined immunodeficiency syndrome her own T cells engineered to carry a normal ADA gene. Similar approaches were conducted to deliver a molecule called tumor necrosis factor (TNF) directly to tumor cells because, in animal models, this toxic agent had destroyed cancer with impressive potency.

Many of these studies involved tumor-infiltrating lymphocytes (TILs), white blood cells that home specifically to cancerous tissue. Today, TILs are the centerpiece of adoptive cell transfer, in which Dr. Rosenberg's team isolates TILs from patients with advanced melanoma, selecting the most potent ones and expanding them outside the body. Because the body's natural immune system is not effective enough, the researchers wipe out many of the nonresponsive immune cells with chemotherapy drugs and replace them with the more effective TILs.

Dr. Rosenberg's persistence has been rewarded. His team has seen objective regression of cancer in 50 percent of melanoma patients for whom all other treatments have stopped working. "Adoptive cell transfer is the most effective immunotherapy for cancer and the only immunotherapy capable of causing that degree of tumor response," he says.

A surgeon by training, Dr. Rosenberg joined the NCI in 1970 as a Clinical Associate, and became Chief of CCR's Surgery Branch in 1974.
Photo credit: Rhoda Baer

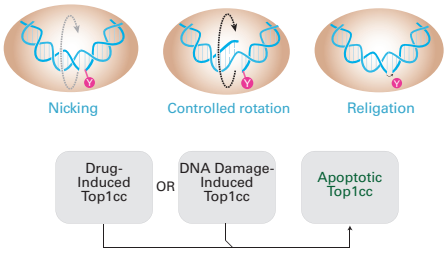
The researchers are refining the approach and working to extend it to more common cancers. In the laboratory, they are isolating the genes that code for T cell receptors that recognize many antigens on common cancers. They use retroviruses to insert those genes into normal T lymphocytes in the laboratory and recruit them to recognize the cancer and go to work. They recently demonstrated that the administration of these genetically engineered cells could mediate the regression of cancer in some patients, the first proof of the principle that gene therapy can be effective in cancer treatment.

Researchers at other institutions—Fred Hutchinson in Seattle, M.D. Anderson in Houston—are beginning to use the approach. "I have every expectation that adoptive cell transfer will be widely applied in this country," Dr. Rosenberg says with confidence and great hope. "Every patient we treat at CCR has a disease that cannot be successfully treated by today's medicine. The patients we see have advanced cancer with very limited life expectancy. We are not here to administer today's treatments; we are here to develop the treatments of tomorrow."

Like the Natural Product, Only Better

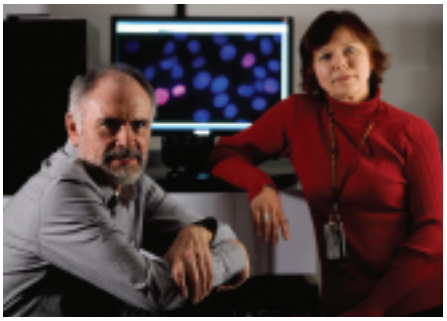
"This couldn't have been done anywhere else."

Top1 Cleavage Complex (Top1cc)



"Imagine DNA as a hopelessly twisted garden hose. Topoisomerase 1 acts like a pair of scissors that cuts the hose and holds both ends while the tangles are removed, then reconnects the two ends so the hose is back in working order," explains Dr. Pommier. "Top1 inhibitors prevent the 'scissors' from gluing back the two ends. The drugs act as a wedge so that the DNA can't settle back into its coiled conformation, and trouble for the cancer cell begins."

Dr. Yves Pommier. *Photo credit: Rhoda Baer*



Dr. William Bonner and Dr. Olga Sedelnikova. *Photo credit: Rhoda Baer*

Topoisomerase 1 (Top1) is an essential enzyme that enables tightly coiled DNA to unwind and open up so that transcription and replication can take place. It then assists the DNA in closing back up again, restoring the DNA double helix. Dr. Yves Pommier, Chief of CCR's Laboratory of Molecular Pharmacology, received an NIH Merit Award for his comprehensive approach to devising drugs that block that action and selectively kill cancer cells.

For a long time, camptothecin, a natural product that comes from the *Camptotheca acuminata* tree, was the only drug that could attack topoisomerase 1. "Our goal was to find more options," says Dr. Pommier. In 1991, his team was the first to propose how camptothecin traps the enzyme and DNA in open conformation. It takes advantage of a key difference between normal cells and cancer cells. "Cancer cells are impatient," explains Dr. Pommier. "They can't hold on while the drugs keep the DNA break open. It's toxic to them. Normal cells have the ability to wait out the damage."

The Pommier team's hypothesis proved correct when they solved the crystal structure of the three-way complex of camptothecin, Top1, and DNA in 2005. They also showed that many naturally occurring anticancer drugs (vinblastine, Taxol™, and rapamycin) and some antibiotics use the same mechanism. "Our data show that researchers should be looking for new agents that stabilize open conformations," Dr. Pommier notes.

Camptothecin is effective, but it has weaknesses. Dr. Pommier and his colleagues set out to find more potent cousins. They searched for drugs that are stable longer in the blood and trap DNA-Top1 complexes in an open conformation for longer periods than camptothecin can. They succeeded. Using NCI cell lines and COMPARE analysis (a chemical and cellular screening database to reveal similar patterns of activity), they searched through thousands of drugs in the NCI's Developmental Therapeutics Program (DTP). "I asked the late Dr. Ken Paull in DTP to look for something that looked like camptothecin," Dr. Pommier says. "We found a group of drugs called indenoisoquinolines. This couldn't have been done anywhere else."

The progress made in developing new Top1 inhibitors was possible because of a strong collaboration between CCR and the Developmental Therapeutics Program, researchers at Purdue University, and private industry. NCI and Purdue now share a patent for these new Top1 inhibitors. Of about 400 indenoisoquinolines found through the NCI screen, eight lead compounds are in high-priority development by NCI. At least one has been licensed to a drug company for further development.

This Biomarker Will Help

Thanks to Dr. William M. Bonner's discovery of a biomarker for the double-strand breaks in damaged DNA, upcoming Phase 0 and Phase I clinical trials of the indenoisoquinolines will be more conclusive. When these breaks in DNA occur, many molecules of histone H2AX quickly become phosphorylated. Dr. Bonner, also in the Laboratory of Molecular Pharmacology, has developed and patented an antibody to phosphorylated H2AX that will enable clinicians to monitor whether the drugs have hit their molecular target and caused DNA damage.

Akt Activation: Lung Cancer's Ally

In cancer, activation of the Akt protein is a common molecular change—it occurs in over half of tumor types tested by CCR's Dr. Phillip Dennis. Importantly, Dr. Dennis' studies suggest that Akt activation occurs early in the development of tobacco-related cancers, such as lung cancer.

This critical protein may soon become a decision-making tool to individualize care for patients with early-stage non-small-cell lung cancer. Measuring Akt activation may help doctors determine which patients need more aggressive treatment. The timing is right, as large lung-cancer screening trials are leading to diagnoses of more patients at this early stage of disease.

And that's just one direction in which Dr. Dennis, Head of the Signal Transduction Section in CCR's Medical Oncology Branch, is heading with Akt. His team moves seamlessly between new drug discovery to development and delivery of therapies and diagnostics to patients in clinical trials at the National Naval Medical Center in Bethesda.

They aim to determine exactly how tobacco components activate Akt in normal lung cells and in lung cancer cells, and why Akt activation seems to empower cancerous cells to escape apoptosis—a form of programmed cell death—and survive even in the face of chemotherapy and radiation treatments.

With answers to these important questions, the scientists will be armed to target the Akt pathway with the next generation of lung cancer treatments and preventive approaches. The ultimate goal, in Dr. Dennis' words, is to "individualize therapy for lung cancer, against which current therapies have an abysmally low chance of success."

Dr. Dennis and his CCR colleagues within the Molecular Targets Development Program have developed a group of Akt pathway inhibitors called phosphatidylinositol ether lipid analogs (PIAs), which scientists in CCR and NCI's Division of Cancer Treatment and Diagnosis have already shown to be active against lung, renal, and prostate cancer cell lines. Studies in animal models also have suggested that PIAs may translate into effective cancer therapies for humans.

Dr. Dennis is not stopping there. He is also conducting preclinical tests of several drugs approved by the FDA for other indications that they can inhibit the Akt pathway. In addition, he is spearheading clinical trials that will evaluate Akt pathway inhibitors in patients with lung cancer as well as with rare conditions, such as Cowden syndrome, who develop tumors with highly active Akt pathways.

Dr. Phillip Dennis and nurse Donna Marie Adams speak with patient Dr. Harry Mangold. *Photo credit: Rhoda Baer*

Dr. Phillip Dennis and doctoral candidate Courtney Granville look at lung tissue. *Photo credit: Rhoda Baer*

Center of Excellence in Chromosome Biology

There is nothing static about the contents of a cell's nucleus. The incredibly dynamic nature of chromatin within the nucleus is becoming clear through research at the Center for Cancer Research. A group of committed CCR scientists has formed the Center of Excellence in Chromosome Biology to consolidate expertise and pursue the impact of their observations about the workings of chromatin.

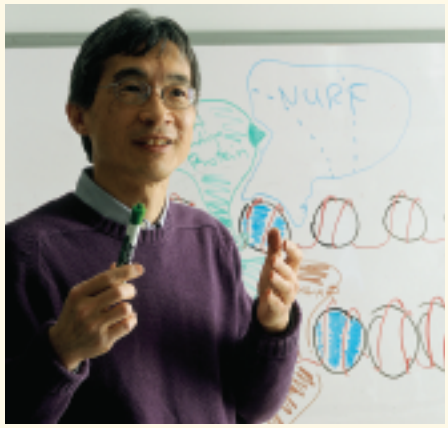
Chromatin in Motion

Dr. Thomas Misteli. *Photo credit: Rhoda Baer*

How are genomes organized in space and time within the cell nucleus and how do cellular gene expression machines such as transcription complexes interact with chromatin in living cells? Dr. Tom Misteli is addressing these questions and obtaining fascinating answers using live cell imaging and computer simulations.

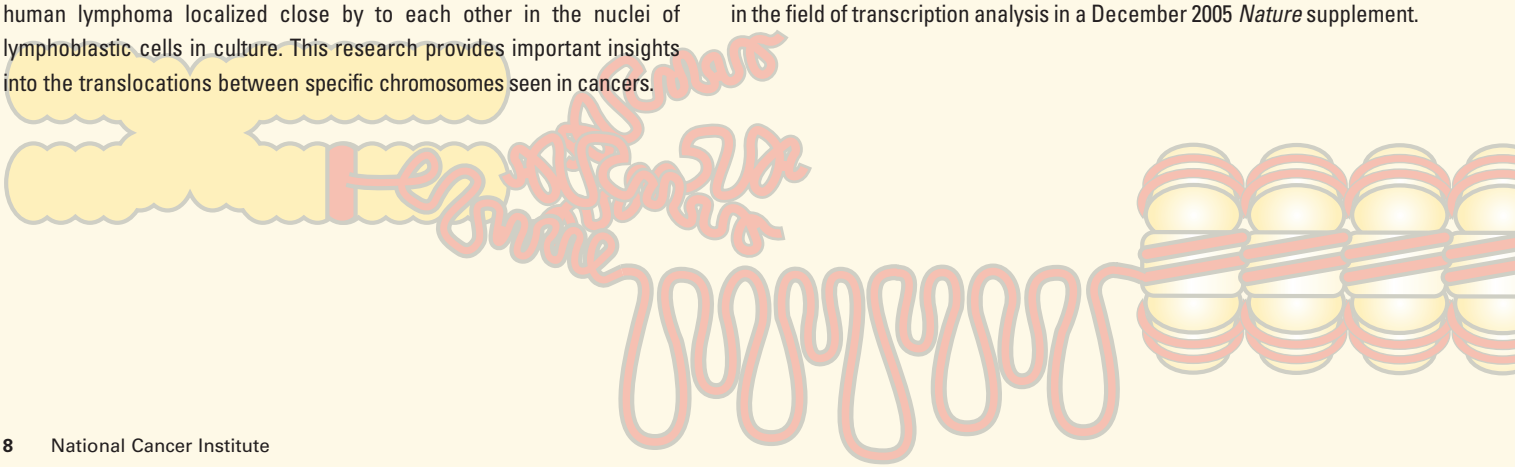
In two landmark papers, Misteli's group visualized a set of mouse chromosomes and analyzed their positions. His team provided evidence that the 3-dimensional spatial relationship among chromosomes is far from random. In fact, chromosomes actually cluster into distinct neighborhoods, depending on the cell type. Misteli's group found that chromosomes 5 and 6, which are frequently involved in translocations in liver cancers, were physically near one another in normal liver cells as well. They further showed that the gene loci involved in translocations in human lymphoma localized close by to each other in the nuclei of lymphoblastic cells in culture. This research provides important insights into the translocations between specific chromosomes seen in cancers.

The Nucleosome Slide



Dr. Carl Wu. *Photo credit: Rhoda Baer*

In the 1990s, scientists suspected that the architecture of chromatin had to be reconfigured for gene expression to occur, but they did not know how it took place at the molecular level. In 1994, Dr. Carl Wu, newly elected member of the National Academy of Sciences, found the answer by devising an elegant assay that captured the changes that occur in chromatin when a transcription factor binds to a gene promoter. Promoters are DNA sequences that are recognized by the enzyme RNA polymerase, the protein workhorse of transcription, and demarcate which genes should be transcribed and, therefore, which proteins the cell will ultimately manufacture. Dr. Wu then tackled another unsolved problem. When nucleosomes change their position so that chromatin has a more open configuration, energy from a molecule called adenosine triphosphate (ATP) is required. He knew that ATP did not bind to the transcription factor directly. Instead, his lab showed that a novel, multiprotein complex he called NURF (nucleosome remodeling factor) is what utilizes the ATP. NURF reshapes the chromatin using the energy provided by ATP. This complex physically slides the nucleosomes aside so that RNA polymerase can bind and enable gene expression. This pioneering series of experiments was cited as a milestone in the field of transcription analysis in a December 2005 *Nature* supplement.



Deoxyribonucleic acid (DNA) is a molecule with a mission—to pass on instructions the cell uses to build proteins essential to life. The complete supply of DNA—all the genes and spaces in between—are packaged as macromolecules called chromosomes, and the sum total of all the chromosomes of a species is called its genome. Each chromosome houses many working units called genes, and each gene sits within tightly coiled DNA strands that are wrapped around eight histones in a package called a nucleosome. Chromatin is the full collection of these nucleosomes. All this is packed into the nucleus of the cell.

Dr. Michael Bustin. *Photo credit: Rhoda Baer*

Ever Changing Chromatin Fiber

The chromatin fiber is metabolically active. This dynamic and flexible structure continuously changes in response to a wide range of biological signals. Dr. Michael Bustin studies proteins that are the major agents of this structural change, the high-mobility group (HMG) proteins and H1 histones. H1 histones stabilize chromatin structure and decrease access to the DNA, while HMG proteins open the chromatin fiber and increase access of DNA to regulatory molecules. Dr. Bustin, together with Dr. Misteli, discovered that HMG and H1 histones are highly mobile and do not remain attached to a specific site of the chromatin throughout the cell cycle, as previously thought. His team demonstrated that HMG proteins compete with H1 histones for binding to chromatin and form a network of dynamic interactions to regulate a cell's response to various signals. Today, using genetically engineered mice, the Bustin team is sorting out the exact functions of these mobile proteins and their putative roles in cancer and other genetic diseases.

Dr. Bustin pioneered the use of immunochemical approaches to the study of the structure and functions of histones and chromatin, providing unique reagents to the broad scientific community before any were available commercially.

Putting the Brakes on DNA Breaks

Dr. Andre Nussenzweig studies a type of blood cancer called B-cell lymphoma, which is linked to chromosomal translocations between an antibody gene and a cancer-causing oncogene called c-myc. Normal B cells routinely make breaks in DNA to recombine genetic information and build proteins that confer specific antibody shapes. But these DNA breaks increase the risk for chromosomal translocations. The Nussenzweig group asked how normal B cells protect themselves against accumulating too many of these DNA breaks and unwanted translocations. They discovered a powerful trio of proteins—ATM, p53, and p19—that apply the brakes in a cell when necessary, keeping deregulated B cells from progressing toward malignant growth.

When breaks accumulate in B-cell DNA, ATM activates the brakes, the p53 tumor suppressor. When the cancer-causing c-myc's protein calls for overactive growth, p53 again is activated. And when ATM is not present to signal for p53, p19 protein steps in to activate p53. The researchers also found that primary B lymphocytes that lack these three proteins have a high level of chromosomal translocations. Either ATM-p53 or p19-p53 complexes seem able to provide braking action, keeping deregulated B cells from progressing toward malignant growth.

Purposeful Repair

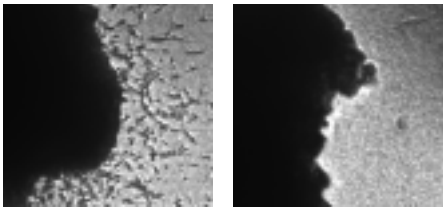
DNA also undergoes purposeful nicks to relax its shape during replication to make new DNA strands as part of the larger cycle of cell growth and division. If unwanted damage to DNA occurs during replication, the cell cycle stops for repairs, and then replication starts up again. Signaling molecules must be able to distinguish purposeful from accidental nicks in DNA. Dr. Michael Lichten is figuring out how the cell discriminates between these two types of nicks.

He found that, when both strands of DNA incur a break, cohesin, a protein that holds the pieces together until mitosis, is quickly recruited to the region around the breaks. The cell phosphorylates a histone called H2AX in the nearby nucleosomes that sends a signal for cohesin to arrive. Interestingly, phosphorylated H2AX and cohesin are absent immediately near the break to leave space for repair proteins and various chromatin-remodeling complexes. Throughout this flurry of repair activity, large remodeling complexes move about the nucleus to sites of DNA damage and the cell cycle temporarily stops. When phosphates are removed from H2AX in the regions that flank the double-strand breaks in DNA, the cell cycle restarts.

Exploiting the Multiple Personalities of NO

"NO" SPECIAL DELIVERY

Dr. Larry Keefer's group synthesizes chemical delivery systems that target NO to specific sites within the human body. The Keefer team encages NO in a prodrug form so that the gas can be released selectively, only when the prodrug gets inside the cell and reaches its targeted compartment. For example, using innovative chemistry, they can deliver encaged NO selectively to liver cells where cytochrome P450, an enzyme that works in the liver, activates the prodrug and releases the gas. This and similar chemical delivery tools developed by the Keefer team are proving useful to unraveling the biology of NO.



+ NO **+ NO + Thrombospondin-1**

Thrombospondin-1 potently inhibits nitric oxide-stimulated angiogenesis of muscle tissue in culture.

AN ANGIOGENESIS SWITCH

In their search for a molecular pathway responsible for turning on angiogenesis, CCR scientists led by Dr. David Roberts found an unexpected pathway that supports a tumor's attempt to create its own network of blood vessels. They found that genes that encode type 1 collagen, a major structural component of cartilage, are also key players in tumor angiogenesis and spread and are regulated by thrombospondin-1. They also showed that strands of stabilized oligonucleotides that bind to and silence the messenger RNAs encoding these collagens genes are potent angiogenesis inhibitors.

Nitric oxide (NO) is a pollutant emitted by automobiles. It is also a vital biological molecule produced by human cells that plays important roles in cardiac health as well as cancer development and, perhaps, prevention. Several CCR groups are joining efforts to study this unstable gas with myriad biological effects. The goal is to manipulate NO levels to fight cancer.

Because there is so much to learn about NO and the oxidation-reduction reaction called redox, CCR formed the Cancer Redox Biology Faculty, chaired by Dr. David Wink, to enhance communication and promote collaboration among biochemists, chemists, clinical oncologists, epidemiologists, and others interested in the molecular mechanisms by which redox stress alters cancer development and tumor spread. Researchers are also working to use imaging techniques to visualize redox status within tumor cells and to use NO to improve treatments for cancer patients. "We are trying to get an idea of the different redox mechanisms affected in cancer and then form collaborations to attack them," said Dr. Wink, who has been studying NO for 15 years. Forward progress has already been accelerated.

Drs. Roberts and Wink were richly rewarded when they turned their multidisciplinary teams toward NO's multiple personalities in angiogenesis. They found that while low levels can stimulate the growth of blood vessels to the tumor, high concentrations inhibit this activity. These two CCR scientists published two papers in the same issue of *PNAS* to share their work, which won recognition for being among the Top NCI Science Advances for 2005. The investigators shed light on the relationship between NO and thrombospondin-1 (TSP1), a potent angiogenesis inhibitor. They demonstrated the existence of dose-dependent, negative-feedback loops between NO and TSP1, which may be exploited to identify unique therapeutic approaches for controlling pathological angiogenesis.

On behalf of the CCR, Dr. David Wink (CCR) presents a lifetime achievement award to Dr. Ignarro (UCLA), one of a trio of researchers who won the 1998 Nobel Prize for the discovery of NO's role as a signaling molecule in the human cardiovascular system.

"Since its discovery, nitric oxide (NO) has acquired a reputation as both friend and foe."

D. Wink, D. Roberts, and CCR colleagues from their award-winning papers: *PNAS*:102(37)2005.

Dr. Wink's lab has also found that inhibiting NO after radiation or chemotherapy can tremendously increase the treatments' efficacy. In collaboration with CTG, an Italian company, NCI is testing hydrogen sulfide-based nonsteroidal anti-inflammatory drugs (S-NSAIDs) in chemoprevention trials for colorectal cancer, comparing them with other redox compounds such as NO-donating aspirin.

An International Challenge: Chronic Graft vs. Host Disease

Transplanting stem cells from a sibling or a matched, unrelated donor into a patient's bloodstream is called allogeneic hematopoietic stem cell transplantation (HSCT), and it is achieving impressive results in curing blood cancers. Yet, up to 40 percent of patients who receive this treatment experience a major, potentially disabling and life-threatening complication called chronic graft-versus-host disease, or CGVHD. Now an NIH-led international initiative is devoting much needed attention to this problem and making striking progress.

CCR's Dr. Steven Pavletic is spearheading the effort to advance understanding of GVHD, which occurs when the donor lymphocytes go beyond attacking the recipient's cancer cells to attacking the patient's normal tissues.

Medical approaches to CGVHD have needed a major update. CGVHD is diagnosed and staged based on decades-old, inconsistent criteria. Standard therapy to prevent CGVHD—drugs called cyclosporine and prednisone that suppress the immune system—is rooted in principles developed in the 1980s and fails to control moderate-to-severe CGVHD in about 50 percent of patients.

The CCR-led, CGVHD study group includes national and international experts who are setting "a whole new foundation for the pursuit of clinical research on this challenging disease," says Dr. Pavletic of CCR's Experimental Transplantation and Immunology Branch. In the last year, the group has published papers on its six major areas of focus: diagnosis and staging, histopathology, biomarkers, response criteria, supportive care, and design of clinical trials. "We have accomplished a critical first step: defining a common language and criteria for diagnosing CGVHD. This will help us to conduct studies and share data," Dr. Pavletic explains.

Dr. Fowler collects cells for his Th2 study.

"A common language will help oncologists communicate more effectively. It will empower drug sponsors to develop new agents to prevent CGVHD. The expert community has taken the first vital steps," says Dr. Pavletic, "toward addressing our patients' tremendous need for new, effective treatments."

A BOOST TO PREVENT GVHD

Dr. Daniel Fowler, Head of the Cytokine Biology Section of CCR's Experimental Transplantation and Immunology Branch, is seeking ways to improve transplantation processes so that donor cells can attack cancer—without causing severe GVHD.

Based on preliminary results from an NIH Clinical Center study of the immunosuppressive drug, sirolimus, plus standard cyclosporine therapy, Dr. Fowler has reason to hope that the two-drug combination will reduce chances of GVHD compared with cyclosporine alone.

In another exciting development, Dr. Fowler's studies suggest that giving a booster of immune cells called Th2 cells from the donor 14 days after the initial stem cell transplant might rally the transplant's cancer-fighting ability while still avoiding GVHD. This booster approach may mean substantially reduced reliance on chemotherapy, and, for the two-thirds of patients who have no family donor, it may open the door to effective transplants through a registry of unrelated donors.

Bone marrow transplant survivors from City of Hope gather for a reunion to celebrate their successful therapy. *Photo was kindly provided by Dr. Steven Forman, City of Hope National Medical Center, Duarte, CA.*

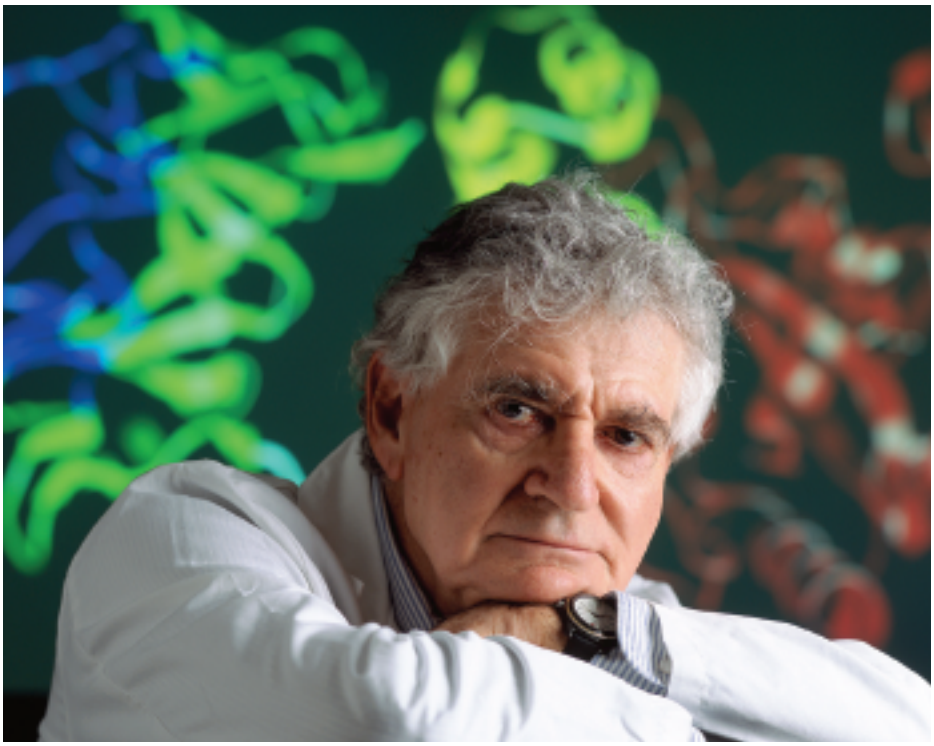
From Rare Cancer to Broader Applications

"We didn't imagine in our wildest dreams that almost all of the patients would go into complete remission."

Dr. Ira Pastan quickly singles out an NCI trial he led in the late 1990s as the most rewarding study of his career. Eleven of 13 patients with hairy cell leukemia whose cancers no longer responded to standard chemotherapy experienced complete remissions. The experimental therapy that made the difference was an immunotoxin called BL22. It selectively delivered a deadly poison to tumor cells, while leaving healthy cells unscathed.

Why is this study so strikingly memorable for a prominent physician-scientist with more than 1,000 published scientific articles? Hairy cell leukemia is a rare cancer, after all, affecting only about 2,000 individuals worldwide each year.

Dr. Ira Pastan. *Photo credit: Rhoda Baer*



The pioneering study was in a favorite research area for Dr. Pastan—using immunotoxins to tackle hard-to-treat cancers—and the results were the stuff scientists rarely accomplish. "We didn't imagine in our wildest dreams that almost all of the patients would go into complete remission," Dr. Pastan said when the remarkable results of the Phase I study were announced. He also knew that hairy cell leukemia was just the beginning.

Dr. Pastan joined NIH in 1959 as an Associate in the Clinical Endocrinology Branch, part of the National Institute of Arthritis and Metabolic Diseases. By 1970 he had moved to NCI, established a Laboratory of Molecular Biology, and become its Chief. His extraordinary accumulation of knowledge is aimed directly at the clinical development of promising new cancer treatments. He has identified proteins uniquely expressed on the surface of cancer cells—notable among them, mesothelin, expressed at very high levels in ovarian and pancreatic cancer and mesothelioma (a cancer affecting the lining of the chest or abdomen)—so that antibodies can be developed that bind only to these proteins. Drugs attached to the protein-targeting antibodies can thus selectively obliterate tumor cells.

The BL22 treatment in the landmark hairy cell leukemia study was a version of *Pseudomonas exotoxin* A—a bacterial toxin on which Dr. Pastan had zeroed in 15 years earlier as a promisingly potent cancer cell killer—genetically modified by Dr. Pastan and fellow NCI scientists Drs. David FitzGerald and Robert Kreitman. The antibody portion of BL22 binds to the CD22

Dr. Pastan inspects his lab's protein purification equipement. *Photo credit: Rhoda Baer*

protein found at high levels on the surface of many kinds of leukemia cells.

Dr. Pastan has developed several immunotoxins that have shown antitumor activity in humans. BL22 and other immunotoxins he developed are being tested in his lab—some in collaboration with academic institutions and pharmaceutical companies—to evaluate their effectiveness against cancers of the ovary, pancreas, and lung, and against glioblastomas, squamous cell carcinomas, mesotheliomas, sarcomas, and various lymphomas and leukemias.

With each animal study and early-stage clinical trial, Dr. Pastan learns more about the structural elements that differentiate cancer cells and how to zero in on them. Among his team's recent advances with immunotoxins:

- Based on the dramatic results of the hairy cell leukemia study, Dr. Pastan tested BL22 in 11 patients with the more common chronic lymphocytic leukemia (CLL), which expresses the same CD22 protein. One patient responded. But laboratory comparison of her cells with those of nonresponders led the scientists to design a more active "high-affinity" version of BL22—dubbed HA22—that should be more effective against more patients with CLL, acute lymphoblastic leukemia in children, and other lymphomas. Early-stage clinical tests of HA22 are planned for next year.

- Dr. Pastan's group, aided by the singular work of Dr. Byungkook Lee, Head of the lab's Molecular Modeling Section, devised a new approach to searching databases to identify new targets for immunotherapy and has identified new targets in prostate and breast cancer and multiple myeloma.

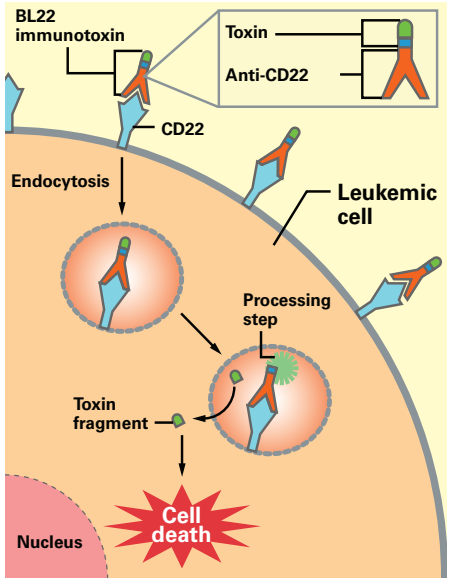
- Dr. Pastan's group devised a technique to use DNA sequences rather than proteins to generate the types of antibodies needed to target cancer cells. This enables scientists to avoid the complex protein purification steps needed to generate antibodies from proteins.

- Preliminary studies from Dr. Pastan's group suggest that the combination of immunotoxins with various chemotherapy agents may "substantially boost" therapeutic effects.

Aided by innovative computer technology, Dr. Pastan and his team are continually working to refine immunotoxins and adjust the way they are given to patients (by continuous versus intermittent administration, for example) so they are more potent and less likely to be inactivated by the patient's own immune cells.

This kind of follow-through is only possible, Dr. Pastan says, because of NCI's steadfast dedication to the leading-edge field of immunotoxin research. "I don't know of another institution in the world," says the scientist, "that would have committed so unwaveringly to this type of high-risk program whose burgeoning promise has been many years in the making."

Art: Jeanne Kelly



Target Mesothelin

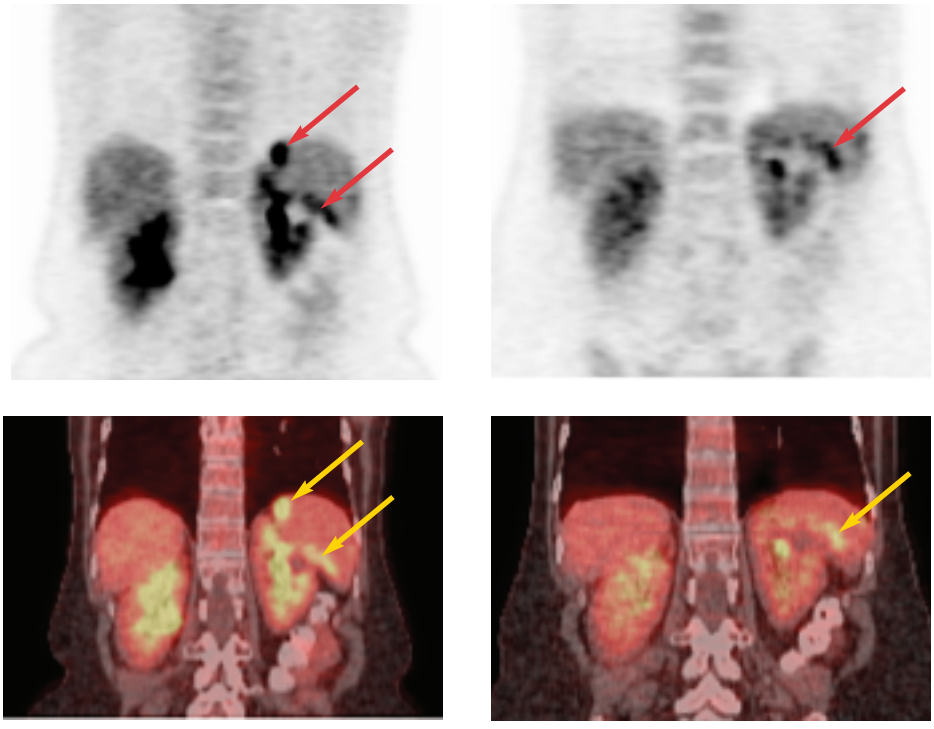
"Twenty-one patients with mesothelioma who were not helped by chemotherapy were treated on this study. Several patients have had clinical benefit with stable disease or decrease in fluid in the abdomen."

Dr. Raffit Hassan has set his sights on turning the protein mesothelin into a bull's-eye that brands cancer cells for annihilation. Mesothelin is found at much higher levels on the surface of tumor cells—including ovarian, pancreatic, and mesothelioma cells—than on normal cells.

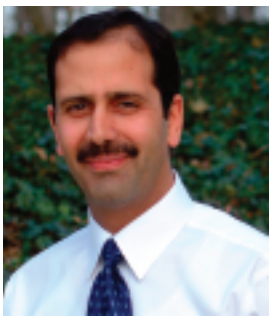
"Mesothelin is a very important molecule for targeted therapies," Dr. Hassan says. He is working with the genetically engineered immunotoxin SS1P, which combines part of an antibody to mesothelin with part of a highly toxic protein called *Pseudomonas exotoxin*. Dr. Hassan, Chief of the Solid Tumor Immunotherapy Section within the Laboratory of Molecular Biology, is leading a Phase I clinical trial of SS1P in patients with mesothelin-positive tumors to collect safety information. He plans further studies to evaluate the drug's antitumor effect. In addition, Phase I testing of MORAb-009, a mouse/human antimesothelin monoclonal antibody, is about to commence at the NCI.

In exciting news for cancer diagnostics, Dr. Hassan's team found that cancer cells with high surface levels of mesothelin often shed the protein into the bloodstream. Using an antibody-based experimental blood test they created, the researchers measured levels of mesothelin in the plasma of many patients with ovarian cancer and mesothelioma as part of a clinical trial under way here at NIH. The findings suggest that the protein might be a tell-tale diagnostic benchmark. The same blood test might also prove useful for monitoring cancer progression and treatment response, so additional studies to validate this test for clinical use are under way.

Patient with peritoneal mesothelioma responds to treatment with SS1P



Before treatment **After treatment**



CCR Investigator Dr. Raffit Hassan chaired the first International Meeting on Peritoneal Mesotheliomas hosted by the NIH Office of Rare Diseases. This recent meeting brought experts together to review the epidemiology, biology, and current surgical and medical management of peritoneal mesothelioma.

Starve the Tumor

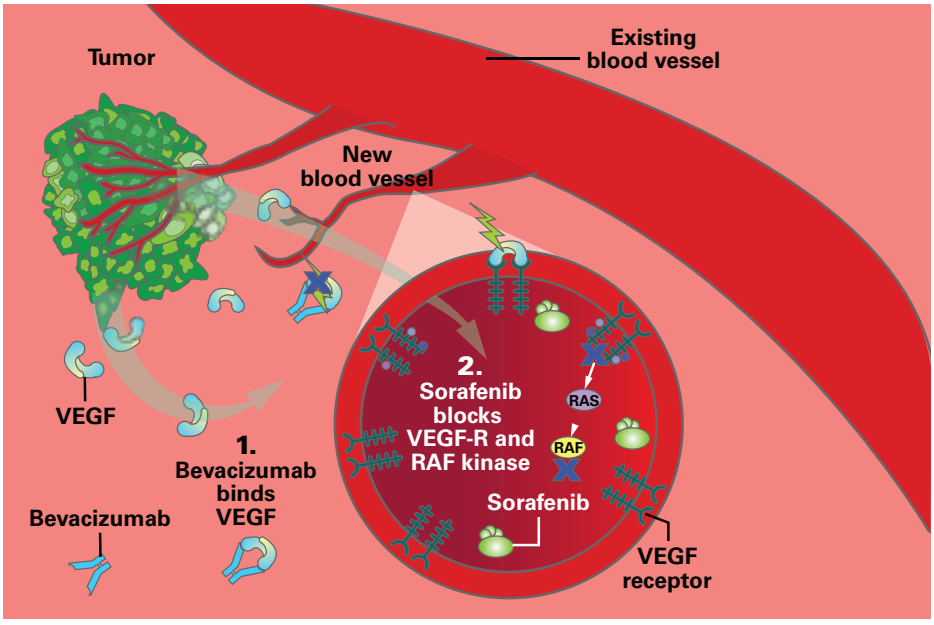
Starve a cancer of the oxygen and nutrients that fuel its growth—Dr. Elise Kohn is taking that approach with ovarian cancer, a rare but deadly malignancy, and several other advanced-stage solid tumors. The Head of the Molecular Signaling Section of CCR's Laboratory of Pathology is leading a Phase I study of the safety and antitumor effects of a combination of two drugs that impede the formation of tumor-nourishing blood vessels.

The drugs, known as angiogenesis inhibitors, are bevacizumab, approved under the brand name Avastin®, for the treatment of advanced colorectal cancer, and sorafenib, approved in January 2006 under the brand name Nexavar®, for the treatment of advanced kidney cancer. Each attacks tumor blood vessels through different mechanisms. "Our hope," Dr. Kohn says, "is that the one-two punch delivered by these drugs will have a superior antitumor effect compared with either one individually."

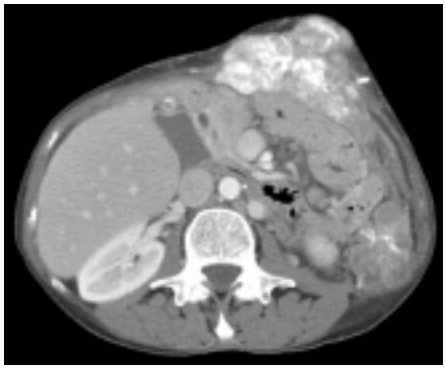
A preliminary look using dynamic contrast-enhanced MRI indicates that the combination reduced the blood supply to many patients' tumors. Also, tumor size decreased in 33 percent of patients with ovarian cancer (some experienced rapid tumor shrinkage), and tumors stabilized in almost all other ovarian cancer patients and in those with colon cancer, melanoma, mesothelioma, and some other cancers. Patients experienced a greater benefit from the drug combination than the researchers expected, with some overlapping toxicity that can be treated with available medications.

Among the follow-up testing on Dr. Kohn's agenda: a close-up look at the patients' tissue samples donated for research using state-of-the-art proteomics technology to look for clues as to how bevacizumab and sorafenib work individually and synergistically.

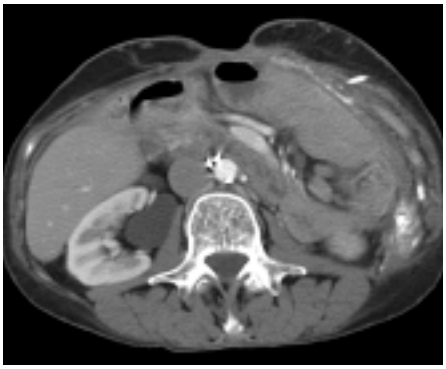
Art: Jeanne Kelly



"Our hope is that the one-two punch delivered by these drugs will have a superior antitumor effect compared with either one individually."



Before treatment

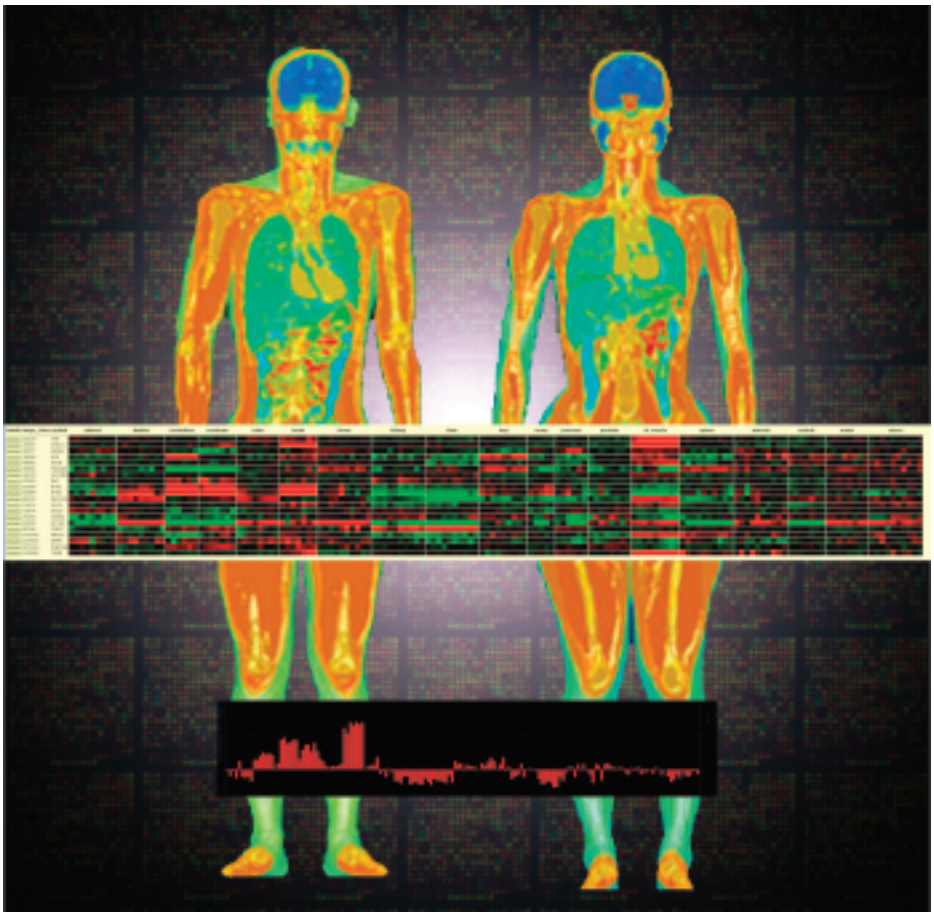


12+ months after one-two punch

As seen on these CT scans, the one-two punch of bevacizumab and sorafenib dramatically reduced this patient's ovarian tumor during Dr. Kohn's Phase I clinical trial of the treatment. The patient's CA125 level, a protein marker in the bloodstream known to increase when cancer recurs, dropped and remained low for more than a year following treatment.

Custom Arrays, Custom Design in Chemistry, Microscale Imaging

Organ Database is available at http://home.ccr.cancer.gov/oncology/oncogenomics and offers researchers a unique tool to better define potential drug targets and to anticipate where in the body they might be expressed. The Organ Database has over 1,000 registered users and has broad NIH-wide and extramural interest.



Gene Arrays

CCR researchers are redefining cancer prognosis by using custom-designed arrays to pinpoint gene expression patterns and other signature characteristics of tumor cells. With CCR colleagues, Dr. Javed Khan, Head of the Oncogenomics Section of NCI's Pediatric Oncology Branch, has developed a method for predicting how patients will respond to treatment for neuroblastoma, the most common tumor in young children. The ability to predict positive and poor outcomes "has major clinical implications," Dr. Khan explains, "allowing us to distinguish a group of ultra-high-risk patients who could benefit from an aggressive alternative to conventional therapy."

Relying on two cutting-edge techniques—artificial neural networks for information processing and computer-based microarray analysis—Dr. Khan's team singled out 19 genes from about 25,000 examined whose expression pattern predicted patient outcome. The Khan group also created and published a database of normal gene expression on the Web so that other researchers can analyze tumor samples against this database.

miRNA Arrays

CCR scientists are also analyzing tumors for unique patterns of expression of microRNA, or miRNAs—small segments of RNA thought to alter the expression of cancer-related genes. A team led by Dr. Curtis Harris, Chief of NCI's Laboratory of Human Carcinogenesis, uses custom arrays to identify miRNA activity in cancer cells and has discovered two miRNAs—has-mir-155 and has-let-7a-2—that may predict tumor aggressiveness in some patients with lung cancer.

Carbohydrate Arrays

In recognition that gene expression is not the only tumor cell marker, investigator Dr. Jeff Gildersleeve, Head of the Chemical Biology Section of CCR's Laboratory of Medicinal Chemistry, is focusing on carbohydrates located on the surface of tumor cells. Carbohydrates are accessible alternative targets for cancer interventions, but the complex makeup of carbohydrates presents a challenge for studying and targeting these molecules. In an early breakthrough, Dr.

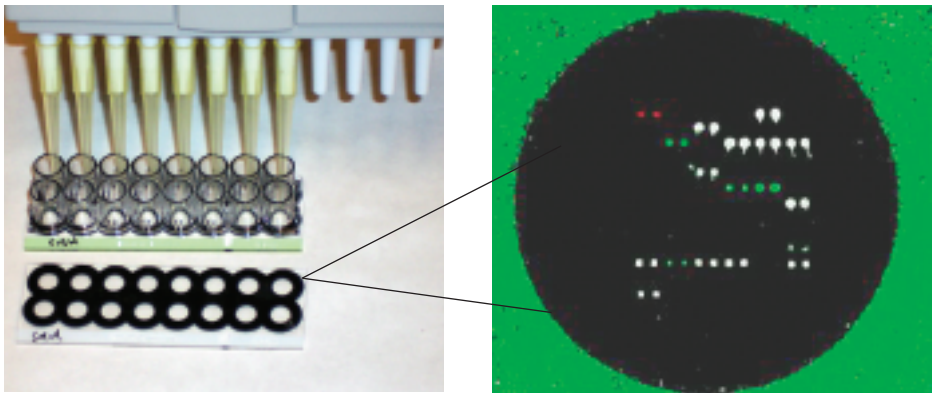
Gildersleeve and his team have developed a microarray that includes 80 different carbohydrates and glycoproteins (complexes made of proteins and carbohydrates). The technology allows for rapid analysis of interactions between carbohydrates and other macromolecules such as proteins, bacteria, viruses, and cells. Applications include monitoring blood serum levels of anticarbohydrate antibodies as diagnostic markers for cancer, development of monoclonal antibodies as diagnostic tools and therapeutic agents, and development of carbohydrate-based cancer and HIV vaccines.

Custom Design in Chemistry

Dr. Pradman Qasba, Head of the Structural Glycobiology Section of the CCR Nanobiology Program, has spent the last several years carefully studying talented enzymes called glycosyltransferases that can add specific sugars to acceptor molecules, such as proteins or lipids, or to the sugar part of glycoproteins, or glycolipids. These sugars, which often face toward the surface of a cell, serve as recognition markers. Using structural knowledge, the Qasba team paid close attention to the regions of the glycosyltransferases responsible for determining what specific sugar to add to the acceptor molecules. They were then able to create a family of designer enzymes capable of adding a sugar of their choice to a wide range of glycoproteins and proteins. These designer glycosyltransferases can now be used to synthesize novel molecules capable of generating nanoparticles linked by sugar chains. These talented transferases can also be used to generate vaccines and to detect specific sugar residues that appear during cellular development and differentiation, and on the surface of tumor cells.

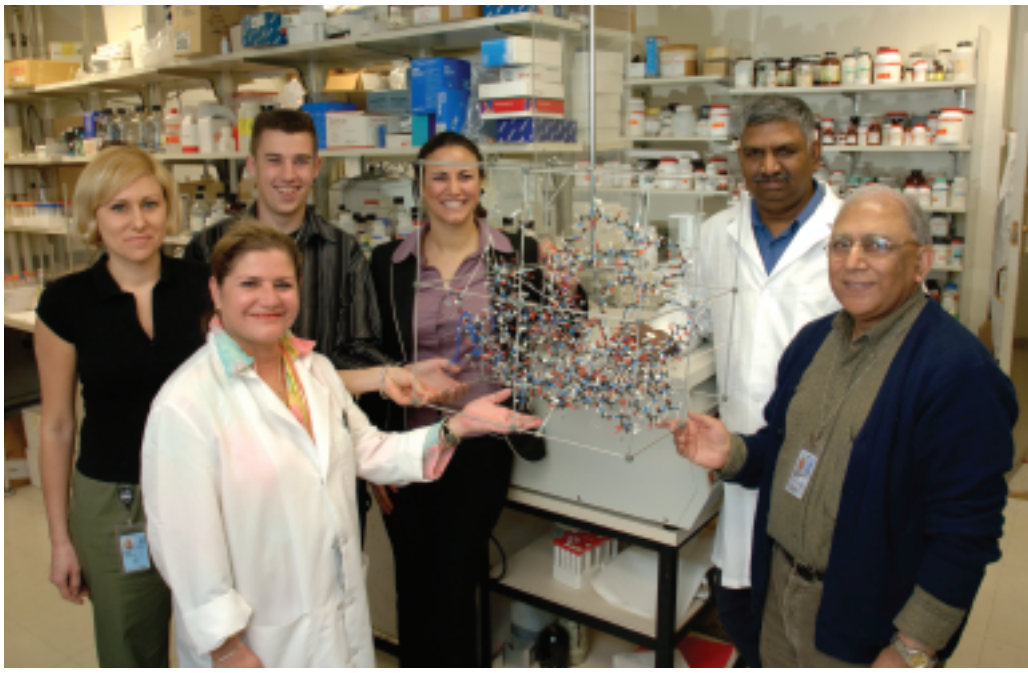
Using nanotechnology to manipulate matter at a remarkably small scale—as much as 10,000 times smaller than human cells—CCR scientists have designed and developed particles that can detect residual tumor. Using these dendrimer-based particles, Dr. Martin Brechbiel with the Molecular Imaging Program produced a

Gildersleeve multiplex set-up and readout



A glass microscope slide fabricated with 16 wells is used for the microarray, and an entire array is printed in each well. The format allows one to carry out 16 individual microarray experiments on each slide. The wells can be removed at the end of the experiment and the glass microscope can be read using a standard microarray scanner.

A fluorescence-based assay is used to determine which carbohydrates are bound by a protein, cell, or virus of interest.



Qasba team

The Qasba team proudly displays the molecular model of beta-1,4-galactosyltransferase. Team members include, from front left to right: Elizabeth Boeggeman and Pradman K. Qasba; and back, left to right: Marta Pasek, Charlton Kilgore, Maria Manzoni, and Boopathy Ramakrishnan. *Photo credit: Bill Branson*

"G6" contrast agent for magnetic resonance imaging (MRI) that may benefit women with breast cancer. His nanosized contrast molecule makes it possible, without surgery, to look for signs of tumor spread to lymph nodes near the breast. The "G6" molecule, so far tested in mouse models of breast cancer, helps visualize lymphatic flow from breast tissue and shows the extent of tumor cell migration into the lymph nodes near the breast—an early sign that the cancer has spread. "Seeing" metastasis would prompt surgical excision of nearby nodes.

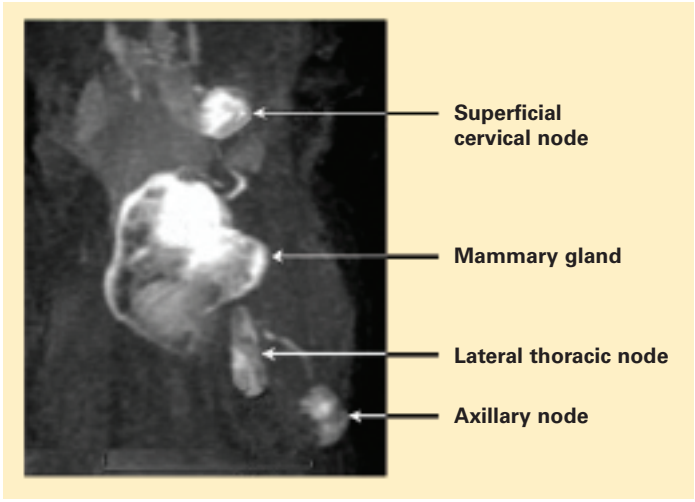
Microscale Imaging

Dr. Sriram Subramaniam is refining techniques to capture the beauty of a cell's architecture in 3-D. He uses an electron microscopy technique called electron tomography (ET) to simulate the molecular-level makeup of protein complexes, viruses, and bacteria.

Dr. Subramaniam, Head of the Biophysics Section of CCR's Laboratory of Cell Biology and a leader in the field of imaging, is improving upon ET with a technique called cryoelectron tomography. Unlike conventional electron microscopy, which requires electron radiation doses so high that they damage biological specimens, cryoelectron tomography is accomplished at very low temperatures, so the Subramaniam team can obtain high-resolution images with very low amounts of radiation and very little perturbation of the specimen.

"Cryoelectron tomography is enabling us to obtain images that fill critical gaps in our knowledge of a cell's internal molecular landscape," says Dr. Subramaniam.

A nonstop inventor, Dr. Subramaniam is devising timesaving tools for the new generation of computerized electron microscopes, including a novel cartridge system that simultaneously loads 100 specimens into the electron microscope. Today that time-consuming work is done by hand. With industry partners, he is developing a novel "dual beam" approach for imaging and localizing nanoparticles in mammalian cells and tissues. While a strong ion beam removes material from the surface in 50 nm increments, a scanning beam images the exposed surfaces. The method can produce images at 10 times the resolution of the conventional confocal microscopy method.



This is an MRI of the mammary gland region of a normal mouse. The nanoparticle contrast agent fills the mammary gland and travels to the nearby nodes and lights up the region. No cancer is present in the gland or in the nodes as evidenced by the bright contrast agent's presence in all locations.

Dr. Subramaniam works with Sang Kim and Jonathan Lefman to help ensure that important imaging enhancements continue in the hands of another generation of talented investigators. Dr. Subramaniam mentors several high school and college students in his laboratory. Students who have trained with Dr. Subramaniam have successfully competed in national science competitions and are studying at top universities and medical schools in the U.S., including MIT, Harvard, Duke, Stanford, UCSD, and Johns Hopkins.

A Multi-Faceted Approach to Brain Tumors

Mouse Models

Dr. Karlyne Reilly has devised mouse models of human astrocytoma brain tumors and human neurofibromatosis type 1, a genetic disease of the nervous system that involves the growth of benign tumors within nerve cells and can lead to malignant nerve and brain tumors. Using these models, the Reilly team is collaborating with scientists in CCR's Nanotechnology Initiative and the Developmental Therapeutics Program to assess the efficacy of new cancer drugs. They are developing new magnetic resonance and bioluminescent imaging techniques to better measure tumor growth and real-time regression after drug exposure.

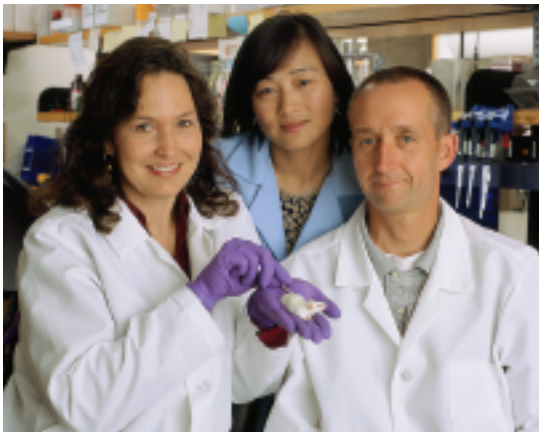
Using these custom-designed mouse models to understand why different individuals may be more or less susceptible to cancer, Dr. Reilly and her team have recently identified astrocytoma and nerve sheath tumor "modifier genes" that influence resistance and susceptibility to tumor development. They are identifying the specific location of these modifier genes. An intriguing recent discovery from their lab is that an individual's susceptibility to these tumors depends on how genes are inherited from the mother or father. This phenomenon occurs by a process called imprinting.

Stem Cell Lines

Dr. Howard Fine, Chief of CCR's Neuro-Oncology Branch, working with his team and NIH collaborators, has found that tumor stem cell lines derived directly from human glioblastoma brain tumors are a better model for studying the biology and physiology of glioblastomas than are cancer cell lines that are commonly used in research laboratories. They also discovered that serumless conditions better preserve the biological integrity and genetic characteristics of these glioblastoma tumor stem cell lines. Said Dr. Fine, "Our in-depth characterization of the biology of glioblastoma tumor stem cells has shown that these tumor stem cell lines may ultimately offer a model system that more accurately represents the biology of the tumors actually found in patients."

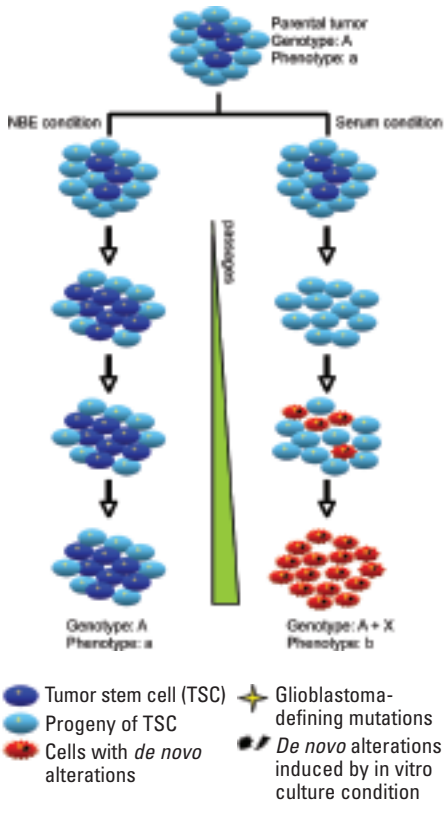
Informatics

Brain tumors are devastating and notoriously difficult to treat. CCR scientists, with partners at NIH and elsewhere, are working to find signature gene expression profiles that point out important distinctions among various brain tumors to develop individual, effective treatments. They are sharing their research broadly through a new, publicly accessible database that will contain molecular, genetic, and clinical data on thousands of patients with brain tumors such as gliomas. Dubbed REMBRANDT (REpository for Molecular BRAin Neoplasia DaTa), the Web-based database will aid collaboration and speed development of targeted therapies. Researchers will be able to explore, for example, how genetic changes link with patients' responses to therapy and survival. REMBRANDT is CCR's contribution to NCI's Cancer Biomedical Informatics Grid (CaBIG), a voluntary grid to share data and analytical tools that accelerate cancer research.



Dr. Karlyne Reilly, Dr. Shirley Tsang, and Robert Tuskan show off their murine collaborator. *Photo credit: Rhoda Baer*

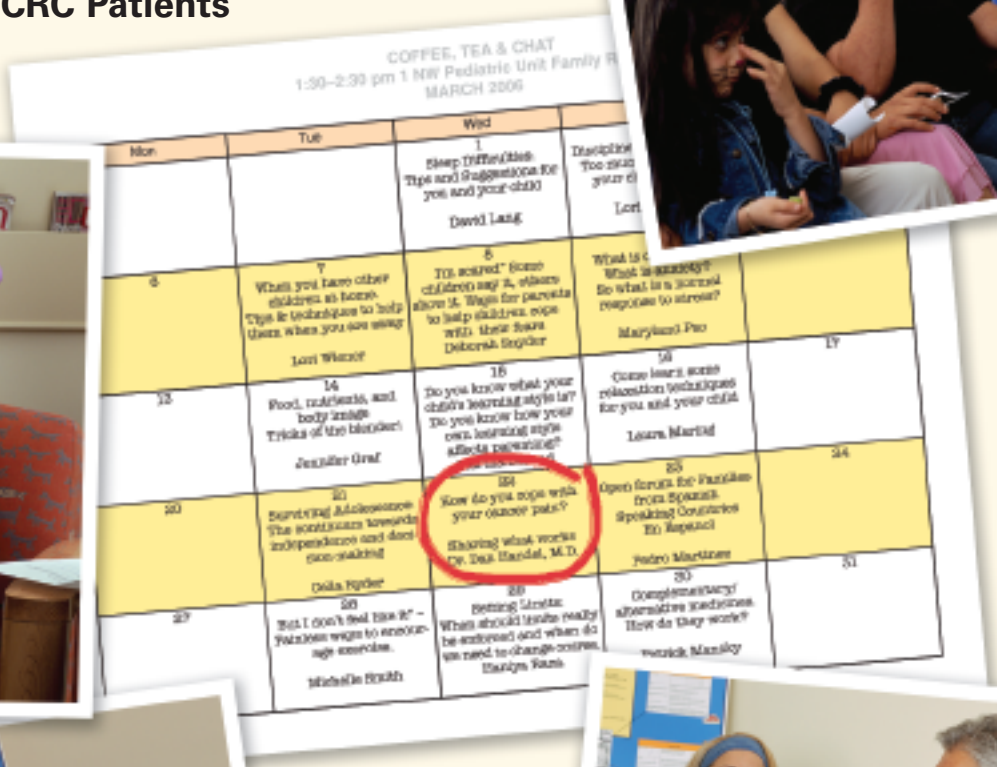
Brain Stem Cell Culture

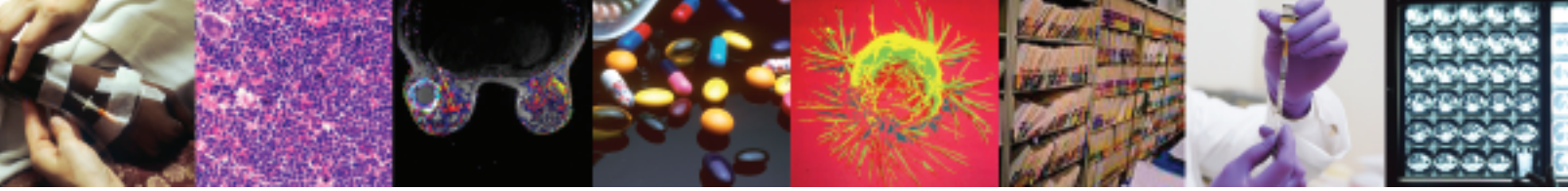


The Coffee, Tea, and Chat Program began at the NIH Clinical Research Center (CRC) in July 2005 to provide a time during the day for families of pediatric patients to come together, meet other families, have some tea and cookies, and learn about issues related to caring for a child with a chronic illness. Parents told CCR's clinical staff what topics they wanted to learn more about related to the care of their children. Twenty "experts" volunteered to participate in this pediatric education program. A few days each week, families gather for an hour for group education and discussion sessions. For those unable to attend, Lori Wiener, Coordinator of the Pediatric Psychosocial Support and Research Program (CCR), provides handouts and keeps available a resource book for parents that is based on the *Chat* topics.

Coffee, Tea, and Chat: Support Group for CRC Patients

Photos: Rhoda Baer





From the Scientific Director for Clinical Research

The Center for Cancer Research takes pride in its clinical research program, an integral component of our nation's cancer program. Distinct from a comprehensive cancer center, the CCR clinical program is a low-volume, high-intensity clinical/translational research enterprise focused on specific diseases. Here, obtaining maximal information from every clinical protocol is a high priority. Virtually all patients followed at the CCR are treated within research protocols. We are dedicated to our patients who voluntarily participate in our clinical trials, and we provide them the most cutting-edge therapies and approaches to treat their disease. This dedication is evidenced by our commitment to learn as much as we can from every biospecimen that they donate.

The wealth of technologies and analysis platforms available today makes it possible to obtain much information from each biospecimen collected. We have developed a centralized facility of human biospecimens for clinical research. We collect material using standardized methods and approaches to ensure the highest quality possible for subsequent analysis. Our newly established Clinical Molecular Profiling Core will support our high-intensity approach by coordinating a complex series of sophisticated genetic and genomic analyses on human samples collected during a patient's participation on clinical trials. The samples will, with patient consent, be procured under NCI's new guidelines for biospecimens, and be subjected to the most advanced technologies to interrogate the disease using as many approaches as are feasible, based on the amount and type of tissue available. We will analyze and mine our acquired data to advance our understanding of the underlying mechanisms and process of disease, and to correlate clinical results with molecular targets and pathways.

Our clinical program is nationally recognized for training strong translational researchers and physician-scientists. The close association between basic and clinical research in a dynamic, collaborative environment fosters advances in both translational research and the development of novel approaches and technologies that benefit the cancer patient. Multidisciplinary and interdisciplinary teams solve complex scientific problems and move discoveries made at the laboratory bench to the clinical setting with enormous success.

As we move into the future, we will focus on testing new treatments that will exploit our improved understanding of disease progression and apply our new understanding to diagnose cancer earlier and treat patients more effectively.

Lee J. Helman, M.D.

The NIH Clinical Research Center provides the world's largest hospital dedicated solely to clinical research. It houses more than half of the NIH-funded clinical research beds in the United States. In fiscal year 2005, more than 1,000 new patients were enrolled on CCR clinical research protocols. All U.S. citizens are potentially eligible to enroll and are afforded easy, rapid access to the clinical trials process through various patient outreach and support services. Medical care is provided without charge and travel costs are covered for patients enrolled on clinical research protocols. For patients younger than 18 years participating in clinical research studies, parent or guardian travel is provided as well. Patients may also come from around the world to participate in CCR clinical studies of rare diseases or cancers. The Children's Inn and the Edmond J. Safra Family Lodge provide housing next to the Clinical Research Center, so that family members of patients undergoing evaluation and treatment can be near their loved ones.

Clinical Trials at the NIH Clinical Center

Clinical research, an integral part of the CCR, is conducted in the new NIH Clinical Research Center (CRC) on the Bethesda campus of the NIH. This facility contains state-of-the-art diagnostic and therapeutic capabilities to support clinical research programs in pediatric and adult oncology conducted by clinical investigators in over 19 laboratories or branches of the CCR. In fiscal year 2005, there were more than 30,000 outpatient visits and over 1,000 inpatient admissions to the CCR clinical research program.

While providing day-to-day care of cancer patients, CCR clinicians train the next generation of radiologists, oncologists, surgeons, pharmacologists, and nurses for careers in clinical research. Several CCR training programs lead to board certification in cancer specialties (see Training, pg. 29).

AVAILABLE CCR CANCER TRIALS

CCR's cancer trials open for enrollment are available at:
http://www.cancer.gov/clinicaltrials

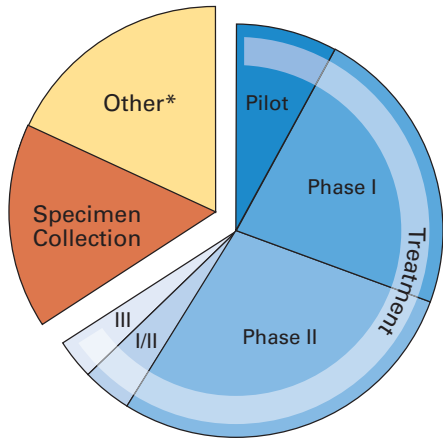
At CRC, CCR scientists translate discoveries at the bench into new diagnostic approaches and new targeted therapies. The researchers use technologies such as genomics and proteomics in their patient-focused approach to treatment research. They are collecting molecular profiles for many cancer types and developing databases that eventually will serve the era of molecular medicine. CCR's clinicians use a science-based rationale for treatment planning. By evaluating a patient's case history and expression profiles of cancerous tissues (when possible) along with evidence-based pharmacological data, clinicians try to match appropriate patients with the available trials. The overarching goal is to diagnose cancers more accurately and treat patients more effectively than is possible with the standard treatment.

Having the lab bench down the hall from the patient's bedside enables CCR scientists to take a new agent that shows promise in an early-phase study and return to the bench to improve its stability, develop a better way to deliver the drug, or design better imaging agents to help monitor its action in the body. Areas of ongoing science-based trials include: early detection, immunotherapy, adoptive cell transfer therapy, molecular targets, innovative combination treatment regimens, drug resistance, local therapy, cancer genetics, and molecular profiling.

New Territory

Approximately two-thirds of the research studies at CCR are testing novel treatments for cancer (see Figure 1). The rest are natural history studies, specimen collection, imaging and screening trials, plus followup, psychosocial, supportive care, epidemiology, and surgery trials. Many of the new treatments are small molecules or biological agents developed at the CCR or in collaboration with academic or industry partners.

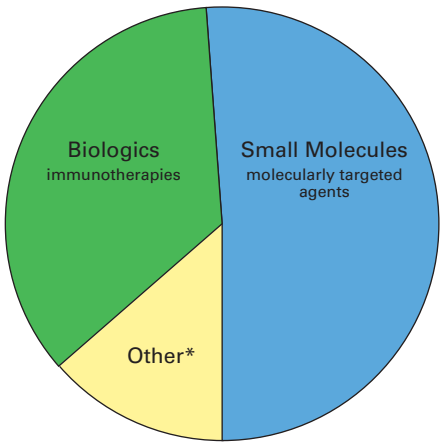
Figure 1



*Natural history, imaging, screening, follow up, psychosocial, supportive care, epidemiology, surgery

The majority of the treatment trials at CCR are early-phase studies. CCR focuses on proof-of-principle research. These small trials answer some of the basic questions about optimizing a new drug's effective dose and manner of delivery. Well before any new agent is placed in a Phase I trial, though, massive preclinical data have been collected and studied carefully in anticipation of moving the treatment to patients. CCR researchers undertake these high-risk, high-impact studies to develop new agents and deliver them as stable, pharmaceutically acceptable compositions. Occasionally, as was the case with Velcade®, a new agent developed by Genentech, CCR improves the compositions for pharmaceutical

Figure 2



*Transplant, cell therapy, radiation, radiofrequency ablation, gene therapy, surgery, exercise

companies that have developed their own promising agent.

Few Phase III trials are done at CCR. Most of those are carried out by cooperative groups at academic medical centers or by the pharmaceutical industry.

New protocol concepts undergo rigorous, timely reviews by relevant boards and committees, and modifications are made as recommended to ensure optimal trial designs that protect patient safety during discovery and refinement of new and effective cancer treatments. The CCR has an administrative infrastructure to oversee and maintain all aspects of the highest quality, ethical clinical research, including regular refresher training in clinical research, patient privacy safeguards, research nursing and data management support, statistical evaluation, and outreach programs to promote and support patient accrual.

A Step-by-Step Process

Clinical trials are research studies in which humans participate. There are several types of trials—treatment, prevention, detection, diagnostic, and quality-of-life. The majority of trials under way in the CRC are treatment trials designed to test the safety and effectiveness of new drugs, biological agents, techniques, or other interventions in people who have been diagnosed with cancer. These trials evaluate the potential clinical usefulness of a therapy or compare an investigational treatment against standard treatment, if there is one. They are conducted in phases.

Phase 0 trials are first-in-human trials involving a small number of patients. They are intended to provide preliminary safety and biological-effect data to optimally inform later-stage clinical development of new therapeutic and imaging agents. The study agent is administered at a low dose for a limited time. These trials are *not* designed to escalate until a maximum tolerated dose is reached.

Phase I trials generally involve a small number of patients. These trials find a safe dosage, decide how the agent should be given, and observe how the agent affects the patient's body. Cancer patients who have no known effective treatment options are eligible for Phase I trials. Study participants are divided into cohorts, and each cohort of participants is treated with an increased dose of the new therapy or technique. Results in early participants greatly influence the dose subsequent participants receive.

Phase II trials are designed to evaluate the effectiveness of the drug in a larger group of participants using the dosage determined to be safe in Phase I trials. On the basis of their findings in Phase I trials, researchers often focus Phase II trials on cancers for which no effective treatment exists and/or cancers that are most likely to show a response to therapy. Some anticancer compounds target molecular pathways in specific cancers; patients with those cancers will be chosen for Phase II trials in order to explore the compounds' targeting mechanisms. If an acceptable percentage of the patients respond well to the drug in a Phase II trial, the agent will go forward to a Phase III trial. Generally, patients who take part in Phase II trials have not found the current standard of care effective or have cancers for which there is no standard treatment.

Phase III trials typically involve large numbers of participants in order to determine whether a new therapy or technique is more effective or less debilitating than a standard treatment. These trials are conducted at multiple institutions around the country, including community settings. The results of Phase III trials guide health care professionals and people with cancer in making treatment decisions.

Like Phase II trials, Phase III trials usually focus on specific types of cancer. Participants enrolling in a Phase III trial are assigned at random to an investigational group that is given the new treatment, or to a control group that receives the current standard treatment. Many people with cancer get their first treatment in a Phase III trial.

Clinical Trials: From Bench to Bedside

	Phase 0	Phase I	Phase II	Phase III
Avg. Years	0.5	1.5	2	3.5
Est. No. of Patients	20	20–100	30–200	150–5000
Purpose	Validate molecular target	Determine safe dose, side effects	Evaluate effectiveness, side effects	Confirm effectiveness, monitor adverse reactions

Compassion at the Cutting Edge of Nursing

RESEARCH ADVANCES HAVE TRANSFORMED CANCER CARE

Fifty years ago, most patients treated for cancer died in the hospital. Much has changed in clinical research and cancer treatment since then. Improved antibiotics and the introduction of growth factors have reduced deaths from infection, and treatment has shifted from broadly cytotoxic drugs that may kill the cancer—but also harm healthy tissues—to more targeted and less caustic chemotherapy and immunotherapy. Oncology nurses have been an integral part of the clinical trials that have brought new and improved care and treatments to people with cancer.

Clinical Center nursing in the 1950s

BROADER, MORE SPECIALIZED CARE

Today, research nurses are on the front lines in clinical oncology, translating the science behind clinical trials into an increasingly specialized yet full range of patient care services. Patients receiving treatment experience a constellation of unpleasant symptoms such as fatigue, anorexia, anemia, weight loss, depression, pain, and sleep disturbance. All of these symptoms can have a profoundly negative effect on quality of life and a patient's ability to receive prescribed treatments. Oncology nurses provide relief from these symptoms based on practice and research. Treatment regimens are much more complicated today than they once were, so oncologists rely on a very specialized workforce of nurses to implement procedures, always keeping patient safety at the forefront. As studies in genetics and genomics yield new diagnostics and improved therapies, highly trained oncology nurses are right there, moving these findings into clinical practice.

"When I started out, patients got their chemo through an IV put in by doctors. Now almost all patients have permanent in-dwelling catheters, and the pumps are complicated. Fifteen years ago, I could flush a line. I wouldn't even touch one any more. As treatment has become more sophisticated, we have all become completely dependent upon our specialized nurses."

Dr. Lee Helman, Scientific Director for Clinical Research, CCR

NURSES AS COMPASSIONATE CAREGIVERS—A CONSTANT THROUGH THE YEARS

Nurses go into oncology nursing because they care about patients with cancer. They want to make the journey as bearable as possible—no matter where a patient is on the journey, from prevention, early detection, cancer control, symptom management, and treatment through survivorship, palliative care, and hospice care. It has always taken a special kind of nurse to work in oncology, and oncology research nurses today play both broader and more specialized roles than they once did. As more and more patients survive their disease, and cancer begins to be viewed as a chronic condition, today's oncology nurses focus their expertise more on nutrition, symptom management, education, patient advocacy, and other quality-of-life issues—treating the whole patient, not just the disease. Oncology nurses carry out their many roles with vision and compassion.

Photo credit: Rhoda Baer

CONTRIBUTIONS ACROSS THE CARE SPECTRUM

CCR nurses bring expertise to the oncology practice in several areas:

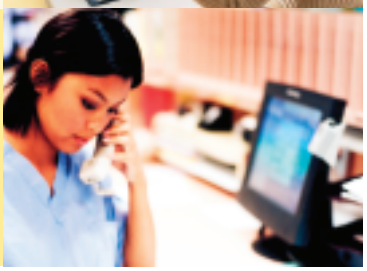
Clinical Research Nurse. Coordinates clinical trials, including evaluating patient eligibility, collecting data, maintaining regulatory documents and requirements, and reporting data to both the investigational review board and the study's sponsor. Also educates patients and other healthcare professionals regarding protocol schema/compliance and monitors patients on the study for side effects, responses, and any other medical issues that arise.

Nurse Practitioner. Performs a variety of medical functions and works under the direct supervision of a licensed physician. Is responsible for performing histories and physicals, and writing problem lists and plans of care for a caseload of patients. Nurse practitioners evaluate protocols, write chemotherapy orders, admit patients to the nursing units, perform specific medical procedures, and handle medical emergencies.

Advanced Practice Nurse in Genetics. Works with patients and families to educate them regarding their diseases and treatment options. Provides genetic counseling to patients and families at high risk for certain diseases, enters patients on clinical trials, trains other healthcare providers in the basics of medical genetics.

Staff Development Nurse. Establishes and implements a staff development program for the Center for Cancer Research (CCR). Serves as a mentor/consultant for CCR staff (RNs, MDs, and data managers), providing guidance on topics such as higher education, certification, professional organizations, publications, career advancement, clinical trials, and regulatory issues.

Patient Recruitment Nurse. Provides detailed information about particular trials to both patients and referring physicians. In some instances, the responsible nurses have patients/physicians send medical reports in advance of their appointment at the Clinical Center to ensure that the appointment is productive. These referring nurses also do a limited amount of eligibility screening over the phone.

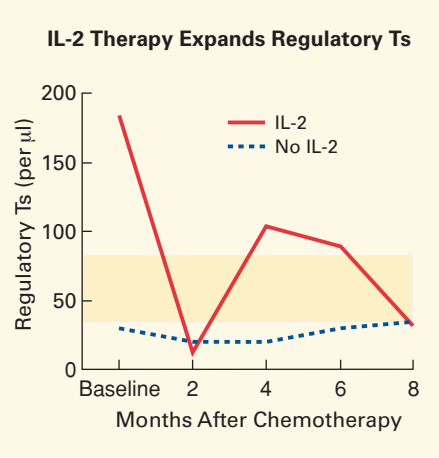


Top three images, photo credit: Rhoda Baer

"Today's oncology nurse enters into a specialty that encompasses many roles—advocate, educator, researcher, and caregiver."

Caryn Steakly, R.N., CCR Deputy Clinical Director

A Shifting Immunotherapy Landscape



In the Mackall lab, Dr. Hua Zhang shows that lymphopenia and IL-2 therapy induce expansion of a subset of regulatory T cells. *Nature Medicine*: 11(11),2005.

The period following chemotherapy has long been considered an optimal time for activating the immune system's white blood cells called lymphocytes to detect and eliminate any remaining cancer cells. According to surprising new findings by CCR scientists, this must be done carefully, by expanding specific subpopulations of lymphocytes and not expanding others.

Research by Dr. Crystal Mackall, head of CCR's Pediatric Oncology Branch Immunology Section, indicates that a condition of abnormally low numbers of white cells called lymphopenia, which often occurs after chemotherapy, actually provides a good environment for proliferation of a subgroup of lymphocytes called suppressor Ts. These suppressor Ts can actually stifle the body's immune response.

The study revealed a second surprise as well: Interleukin 2 (IL-2), a potent immune system activator, can increase the population of these suppressor Ts along with its many other effects. "These data have led to a fundamentally improved understanding of the immune system's complex response to chemotherapy," explains Dr. Mackall. "This discovery is highly relevant to the design of immunotherapies."

Dr. Crystal Mackall and Dr. Aviva Krauss make single cell suspensions of spleens, which were previously transplanted into mice, to evaluate whether they successfully engrafted. This helps them develop better transplant conditioning regimens. *Photo credit: Rhoda Baer*

The Mackall team examined immune recovery in 26 children with pediatric sarcoma, a cancer of the bone or soft tissue. These young patients had received cyclophosphamide-based chemotherapy, which depleted their infection-fighting lymphocytes. When the patients' white cell counts reached a state of lymphopenia, they were given back their own lymphocytes, which had been frozen and stored before chemotherapy began.

In an unexpected finding, patients whose lymphocytes were added back along with IL-2 following their chemotherapy had a marked increase of suppressor T cells.

Dr. Mackall's team also discovered that the suppressor Ts that appeared after the chemotherapy-IL-2 one-two punch grew from a subpopulation of T cells that had survived the patient's drug treatment. So the Mackall group can now explore whether depleting these surviving suppressor T cells could enhance the patient's immune system, making it highly reactive and responsive to antitumor vaccines—and therefore better able to fight cancer. CCR plans a follow-up clinical trial to test this hypothesis, hoping to improve how oncologists rebuild patients' depleted immune cells after chemotherapy.

"We are enthusiastic to follow up on the new, remarkable insights we have gained into what makes the body's T cells take action," Dr. Mackall says. "We are hopeful that new immune stimulators, such as IL-7, may restore T cells more quickly after chemotherapy without giving suppressor Ts the advantage that IL-2 does."

Tackling Breast Cancer With Transplantation

Using immune cells from a sibling, Dr. Michael Bishop, M.D., and his team have been able to shrink tumors in patients with metastatic breast cancer. This is the first time researchers have clearly demonstrated that donated immune cells could act against breast cancer.

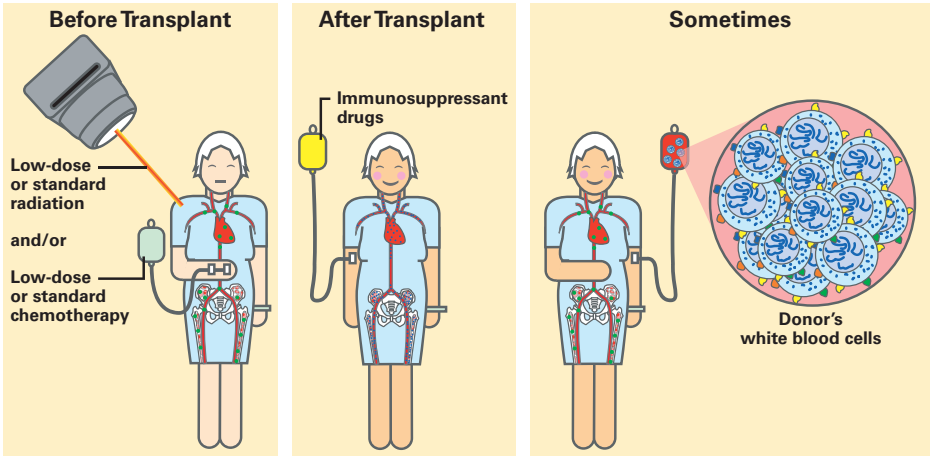
Each of the 13 patients had already been through multiple treatments for metastatic breast cancer. For this study, first, the patient's immune system had to be suppressed so it would not reject the donated immune cells. Chemotherapy drugs were used to wipe out their immune cells. Then stem cells from the blood of HLA-matched siblings were given to the patient. HLA-matched donor cells have the same set of proteins on their surface as the patient's own cells, so they are much more likely to be accepted by the patient's body. The stem cells begin to rebuild the patient's red blood cells, platelets, and white blood cells. A new immune system starts to arise.

Later the patient receives extra T cells from the sibling. T cells are specialized immune cells that recognize and kill foreign cells, such as cancer cells. This two-step approach—first stem cells, then T cells—makes the patient's body receptive to the T cells because it has already become used to the sibling's stem cells. The researchers are then able to attribute any tumor regression to the T cells rather than the chemotherapy.

Next, the scientists will begin a study in as many as 36 patients to see if they can go beyond tumor shrinkage to improve survival. Bishop's collaborator, Daniel Fowler, M.D., is manipulating T cells to maintain their ability to kill tumors while reducing the likelihood that the patient will reject the T cells. This way, the T cells can be given immediately after the chemotherapy.

This approach holds potential for other solid tumors as well.

Dr. Bishop and the clinical team check on the condition of their patient. *Photo credit: Rhoda Baer*



Artwork by Jeanne Kelly. © 2009.

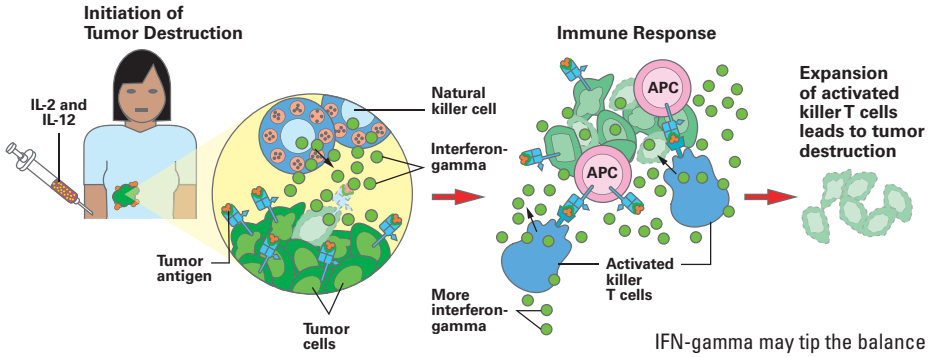
Before infusing donated blood-forming stem cells, the patient receives low-dose or standard-dose chemotherapy and/or radiation therapy. Afterward, the patient is given immunosuppressant steroid drugs to help prevent the body from rejecting the transplant. Sometimes, the patient also receives an infusion of donated immune cells.

Bringing Clarity to the Role of Cytokines

A new combination of two cytokines, chemical messenger proteins that carry signals between immune system cells and the rest of the body, has moved into clinical trials thanks to the work of CCR scientists in the Laboratory of Experimental Immunology. Discoveries about interleukin 2 (IL-2) and IL-12 and the complex workings of the immune system in response to cancer are adding important insights and yielding promising treatment options.

"Depending on other factors in a tumor's microenvironment," says Dr. Robert Wiltrout, Chief of the Experimental Therapeutics Section, "the same protein can favor or hinder the antitumor immune response within the microenvironment." Dr. Wiltrout, whose research team is testing IL-2—an agent already approved by the Food and Drug Administration for treatment of advanced kidney cancer—in combination with either the influential cytokine IL-12 or the anti-CD40 antibody, a molecule that can activate antigen-presenting cells and is expressed on some tumors.

Dr. Wiltrout, Eilene Gruys and Jeff Subleski review their data. *Photo credit: Rhoda Baer*



IFN-gamma may tip the balance toward immune recognition and tumor destruction.

He and his research partner, Dr. Jon Wigginton, formerly of CCR's Pediatric Oncology Branch, have performed preclinical studies in mouse models of metastatic kidney cancer that have shown synergy between IL-2 and IL-12. And the impact is twofold: Tumors grow at a slower rate and, surprisingly, they lose their all-important blood supply as immune cells are recruited to attack the tumor blood vessels. In addition, Dr. Wigginton has been studying IL-12 in mouse models of advanced neuroblastoma, a nervous system cancer usually affecting children. Treatment with IL-12 inhibits activation of Akt, a "prosurvival" protein that helps tumor cells avoid cell death, or apoptosis.

Based on these promising data, Dr. Wigginton has partnered with Dr. John Janik of CCR's Metabolism Branch to perform a Phase I clinical trial at the NIH Clinical Center in which IL-2 and IL-12 are given to patients with advanced solid tumors. Preliminary results include reduced or stabilized tumor size and an enhancement of immune cells, the T and NK cell compartments, in some patients.

Dr. Wiltrout's group also has witnessed synergy between IL-2 and the anti-CD40 antibody against metastatic kidney cancer in mice. This combination mobilizes both killer T cells and antigen-expressing cells, and leaves cured mice resistant to subsequent challenge by the same tumor type.

The antitumor effects of these combinations of biological agents—IL-2 with either IL-12 or anti-CD40—appear to depend on the presence of another protein called interferon-gamma (IFN), which often boosts the body's infection-fighting power. Based on these and other intriguing data on the complex role of IFN in immune response—including a finding that many tumors have IFN receptors that can trigger biological changes when they are exposed to the cytokine—Dr. Wiltrout's team is working to clarify the roles of IFN and other cytokines and cytokine receptors in the immune response to tumors. His research team has hypothesized that IFN can either promote tumor growth and metastasis, or tip the balance toward immune recognition and tumor destruction, depending upon critical events in various tumor and organ microenvironments "A better understanding of these complex events may well lead to more effective biological therapies," concludes Dr. Wiltrout.

Teaching the Art of Inquiry

The Office of Training Education, headed by Dr. Jonathan Wiest, is an integral part of the CCR mission to support young scientists as they become independent researchers. In addition to managing about 900 postdoctoral and 150 postbaccalaureate students, the program supports the next generation of clinical investigators, minority researchers, and high-school and college students who come to CCR to work as summer interns.

Individuals at every level of training experience scientific enrichment. CCR investigators-in-training have access to advanced technologies and computational services along with exceptional online library resources to fortify their pursuit of cancer's biology. They are groomed in the essentials for the conduct of ethical and informative clinical and laboratory research and in the skills needed for lab management. They also receive training in writing professional papers and presenting their data. The CCR has taken several steps to broaden the training experience across the NIH campus. Investigators can participate, for example, in translational fellowships in molecular pathology, radiation sciences, biostatistics, or chemistry.

CCR's labs and clinics at the clinical center are equally important training grounds for clinical fellows—young oncologists, radiologists, and surgeons who have decided to specialize in cancer care. They come to NCI for rotations (up to 3 years) that permit them to combine clinical experience with investigator-initiated research in nearby labs.

Training opportunities for clinical fellows include:

- **ACGME Clinical Residency in Anatomic Pathology**—offers training and research opportunities in anatomic pathology, emphasizing the art of establishing clinical correlations to disease mechanism.
- **ACGME Medical Oncology Fellowship**—provides translational research training in medical oncology. Fellows develop their expertise over a 3-year period. This is the oldest training fellowship in the intramural program.
- **ACGME Pediatric Hematology/Oncology Fellowship**—pairs the Johns Hopkins University and the NCI Pediatric Oncology Branch to prepare researchers adept in laboratory and/or clinical research in this area.

Some resources useful to CCR's postdoctoral scientists include:

- **Fellows Editorial Board**—run by the fellows, provides editorial services and review for scientific papers.
- **Translational Research in Clinical Oncology** (**TRACO**) is a course for postdoctoral fellows to enable strong collaboration between basic and clinical scientists to develop novel approaches for the treatment of cancer. This Web-cast course also has been adapted for training young investigators in Spain.

CCR POSTDOCTORAL FELLOWSHIPS AND TRAINING PROGRAMS

ACGME Clinical Residency Programs:

- Residency in Radiation Oncology
- Residency in Anatomic Pathology
- Residency in Dermatology

ACGME Clinical Fellowship Programs:

- Medical Oncology
- Johns Hopkins University/ NCI Pediatric Hematology/Oncology
- Hematopathology
- Cytologic Pathology

Additional Clinical Fellowship Programs:

- Surgical Oncology
- Urological Oncology
- HIV and AIDS Malignancy
- Gynecologic Oncology
- Neuro-Oncology

Translational Fellowships:

- Multidisciplinary Fellowship in Breast Cancer Research
- Gynecologic Cancer Foundation/ NCI Fellowship in Gynecologic Oncology
- Postdoctoral Fellowships in Radiation Sciences
- Biostatistics/Mathematics Training Fellowship (Informatics Training Program)
- Program for Interdisciplinary Training in Chemistry (PITC)
- Comparative Molecular Pathology Research Training Program
- University of Cambridge/ GlaxoSmithKline Oncology Fellowship

Basic Science Fellowships:

- Cancer Research Training Awards
- Visiting Fellow Program

Success, Sweet Success

From high school students…

Under the Werner H. Kristen Internship at NCI's Center for Cancer Research, high-school juniors and seniors from the Frederick, MD, area work as scientific interns in the CCR labs located there. They work full-time for 9 weeks during the summer followed by 3 hours per day during the school year as student volunteers.

"My internship at CCR strengthened my interest in science. In college I plan to study chemical or biomedical engineering and will use the many research techniques that I learned during my year-long internship. CCR's unique environment was unlike any I could find in a high school classroom. I consider it a privilege to have worked on a real-life problem, to have done meaningful research in one of the nation's top research centers."

— Charlton Kilgore

Charlton is entering the University of Maryland at College Park to study Chemical and Biomolecular Engineering.

…to postdocs…

The Cancer Research Training Award (CRTA) is the CCR's fellowship program to train aspiring scientists. Students in high school, college, graduate school, and medical school, as well as med school grads, who are U.S. citizens or non-U.S. citizens with a permanent resident card are eligible.

"As a postdoctoral fellow at the NCI, I benefited tremendously from a strong institutional commitment to postdoctoral training and excellent mentorship from topnotch scientists. I received the support and training I needed to successfully develop skills, achieve my research goals, and become an independent researcher. In addition, the opportunity to participate in CCR's postdoctoral fellows association made me aware of the challenges facing a burgeoning scientist crystallographer. I am grateful for the tactics I learned to help overcome barriers to my success, and I am sure that the connections I made at the Center for Cancer Research will continue to enrich the rest of my scientific career."

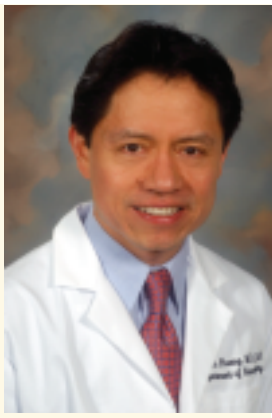
— Nicole LaRonde-LeBlanc, Ph.D.

Dr. Nicole LaRonde-LeBlanc, postdoctoral scientist in CCR's Macromolecular Crystallography Laboratory, won the 2005 Federation of European Biochemical Societies Journal Prize for her outstanding paper on the structure and activity of the atypical serine kinase Rio1. She traveled to FEBS's 31st Congress in Istanbul, Turkey, where she presented her work. Dr. LaRonde-LeBlanc begins a new career as an Assistant Professor of Biochemistry at the University of Maryland at College Park.

…to physician scientists

The highly competitive NCI Scholars Program provided training designed to encourage exceptionally well qualified new investigators to establish themselves as cancer researchers. NCI Scholars received intramural funding at the Center for Cancer Research followed by 2 years of extramural support.

"During my professional development as an NCI Scholar at CCR, I valued most the unparalleled resources offered to me as a young investigator trying to establish my own research program. My experience was indisputably one of the best of my life. I established fruitful collaborations and great support as I enriched and expanded my research without having to struggle for grants."



— Eric Huang, M.D., Ph.D.

Dr. Huang is now an Associate Professor of Neurological Surgery at the University of Utah School of Medicine in Salt Lake City.

In Memoriam: Anita Roberts

Dr. Anita Roberts, a member of the NCI intramural community for 30 years, died on May 26 after a more than 2-year battle with gastric cancer.

Dr. Lalage Wakefield, who worked in Dr. Roberts' lab for 23 years, remembers her mentor's lasting impact on cancer research and her colleagues.

"Anita Roberts was an exceptionally complete human being—one of the top scientists in the world, and a radiantly wonderful personality. She showed us that it's possible to integrate personal and professional lives to the enrichment of both. One of Anita's most amazing achievements was that she managed to take a large and diverse group of people—more than 70 people from over ten nations, many backgrounds, plenty of egos—and actually make us feel and function like a family. She fostered a unique lab culture of friendliness and cooperation, and seemed to take more pride in the lab spirit than in all the academic prizes and accolades she received.

Anita's enthusiasm for science was completely infectious, and she loved working at the bench. She had a pervasive sense of wonder at the workings of the natural world and this infused her quest to understand the molecular basis of disease. Anita co-launched the field of TGF-β research in a hugely productive 20-year collaboration with Dr. Michael Sporn, now at Dartmouth Medical School. Together, they discovered and characterized TGF-β and established its role in autoimmune disease, fibrogenesis, carcinogenesis, and wound healing. Their joint collaboration with Genentech, Inc. to clone TGF-β was a pioneering effort that represented the first formal collaboration between the NCI and a biotechnology company, and it set the stage for many subsequent productive interactions between the NIH and the private sector.

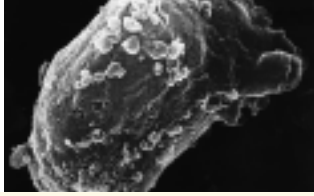
Many of Anita's papers have contributed to radical changes in thinking within the field. She played a critical role in the early work showing that, despite its discovery as a factor associated with carcinogenesis, TGF-β is present in normal tissues and plays key roles in normal physiology. These observations opened up a whole area of research on TGF-β in wound healing, where she was particularly active. Anita leaves an indelible mark on biomedical research, and lives on through her impact on the lives and work of those of us who had the good fortune to know her."

"During my entire career, I never worked with anyone better than Anita Roberts. She was a unique combination of insightful scientist with a razor-sharp intellect and a very sweet person. We had many happy times together in the lab, and her enthusiasm for having a good time while working hard was infectious."

Michael Sporn, Dartmouth Medical School

"As basic scientists, we're all driven by our excitement in finding answers. We hope it ends up as something that becomes therapy. But that doesn't happen unless you have a basic understanding of the process. And that's what my work is all about."

Anita Roberts, in an interview in *Cancer Research* (Spring 2006).



HIV/AIDS Research at the NCI: 25 Years of Progress

THE 1980s

1981 Treated first AIDS patient at the NIH in Metabolism Branch, NCI.

1984 Demonstrated HIV-1 causes AIDS for first time.

Started large-scale production of HIV-1 to develop diagnostic tests.

Developed first diagnostic blood test for AIDS.

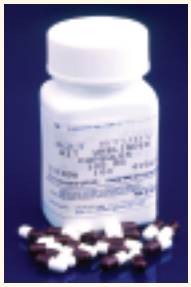
1985 Determined nucleotide sequence of HIV-1.

Demonstrated that AZT (zidovudine) blocks HIV-1 infection.

Dr. Broder introduces AZT

Identified other dideoxynucleosides, including dideoxyinosine (ddI, didanosine) and dideoxycytidine (ddC, zalcitabine), as having anti-HIV activity.

Treated first HIV patient with AZT (zidovudine).



AZT blocks HIV-1 infection

1986 Treated first HIV patient with ddC (zalcitabine).

1987 Received FDA approval for AZT as first drug to treat HIV infection.

Began first drug combination study (AZT and ddC).

1988 Reported first clinical study of AZT in children.

Treated first HIV patient with ddI (didanosine).

1989 Solved structure of an inhibitor bound to HIV-1 protease.

THE 1990s

1991 Received FDA conditional approval of ddI (didanosine) as second AIDS drug.

1992 Demonstrated the presence and functional significance of host cell-derived proteins incorporated into HIV-1.

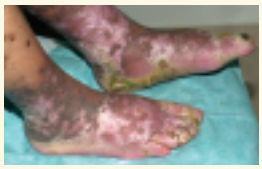
Received FDA conditional approval of ddC (zalcitabine) as AIDS drug.

1993 Solved first structure of HIV-1 reverse transcriptase bound to double-stranded DNA.

Identified nucleocapsid protein as a target for chemical inactivation of HIV-1.

1995 Defined mechanisms of HIV-1 reverse transcriptase drug action/resistance.

Established AIDS Malignancy Consortium to develop approach for the management of cancers in HIV-positive individuals.



Karposi sarcoma lesions

Reported paclitaxel as active against Kaposi's sarcoma.

Linked AIDS data and Cancer Registries.

Established AIDS Cancer Specimen Resource to distribute tissues from AIDS patients for basic, translational, and epidemiological research.

1996 Detected novel herpes virus implicated in AIDS-associated malignancies, including Kaposi's sarcoma, and AIDS-associated lymphomas.

Established HIV and AIDS Malignancy Branch for intramural research in AIDS-associated malignancies.

Solved first structure of HIV-1 integrase with a complete active-site loop.

1997 Reported Cyanovirin-N as the first HIV-1 entry inhibitor.

Received FDA approval for paclitaxel against Kaposi's sarcoma.

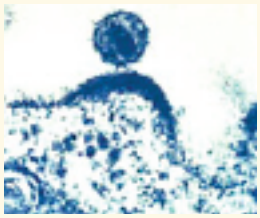
1998 Developed candidate AIDS vaccine based on chemically inactivated virus.

THE 2000s

2002 Demonstrated that individuals with CCR5D32 mutation have reduced HIV-1 susceptibility in humans; those with a low expressor IL-10 allele have reduced risk of developing AIDS-related NHL.

2003 Provided evidence from clinical trials that some AIDS NHL cases are highly curable.

Demonstrated PA-457 can potently inhibit HIV-1 maturation.



Budding HIV

2004 Identified first potent and selective inhibitor of HIV-1 ribonuclease H.

Produced evidence that HHV-8 infection modulates the expression profile of endothelial cells.

2005 Developed ultrasensitive assays to detect patient virus and drug resistance.

Established Office of AIDS Malignancy Program at the NCI.

2006 Demonstrated interleukin-12 is active against HIV-associated Kaposi's sarcoma.

Web Sites With More Information About CCR

CENTER FOR CANCER RESEARCH

http://ccr.cancer.gov

Office of the Director
http://ccr.cancer.gov/about/default.asp

Office of the Clinical Director
http://ccr.cancer.gov/trials/clinical_director.asp

Office of Communications
http://ccr.cancer.gov/news/ooc.asp

Office of Science and Technology Partnerships
http://ccr.cancer.gov/research/ostp/

Office of Training and Education
http://ccr.nci.nih.gov/careers/office_training_education.asp

PATIENT INFORMATION ON CANCER AND CLINICAL TRIALS

Open NCI Clinical Trials
http://www.cancer.gov/clinicaltrials

How to Refer a Patient
http://bethesdatrials.cancer.gov/professionals/refer.asp

NCI Cancer Information Service
http://cis.nci.nih.gov/
1-800-4-CANCER (1-800-422-6237)

Understanding Cancer Series
http://www.cancer.gov/cancertopics/understandingcancer

Clinical Studies Support Center (CSSC)
http://ccr.cancer.gov/trials/cssc/staff/services.asp

ADDITIONAL LINKS

National Cancer Institute (NCI)
http://www.cancer.gov

Working at the NCI
http://www.cancer.gov/aboutnci/working

National Institutes of Health (NIH)
http://www.nih.gov

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